ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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ORGANIC SYNTHESES

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PREFACE TO VOLUME V

THE general plan of this series has been made clear in the earlier volumes. In this volume twenty-four of the thirty-three preparations have been submitted by eighteen contributors, thus showing a cooperation of organic chemists both in this country and abroad which is greatly appreciated by the editors.

Directions are included for the isolation of two amino acids from natural products and it is hoped that other preparations of this type will appear in future volumes.

In accordance with the general policy of including any improved directions for methods included in the previous volumes, a new set of directions for the preparation of ethyl oxalate is given in this volume.

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ORGANIC SYNTHESES

I

p-ACETAMINOBENZENE SULFINIC ACID

$$(p)\ CH_3CONHC_6H_4SO_2Cl + Na_2SO_3 + H_2O \rightarrow$$
$$(p)\ CH_3CONHC_6H_4SO_2H + NaCl + NaHSO_4$$

Submitted by S. SMILES and C. M. BERE.
Checked by HENRY GILMAN and F. SCHULZE.

1. Procedure

THE crude p-acetaminobenzene sulfonyl chloride (p. 3) obtained from 67.5 g. (0.5 mole) of acetanilide is shaken for two hours with a solution of 250 g. (1 mole) of crystallized sodium sulfite ($Na_2SO_3 \cdot 7H_2O$) in 500 cc. of water. The reaction mixture is kept slightly alkaline by the addition at intervals of small portions of 50 per cent sodium hydroxide solution. The total volume of alkali used varies from 10 to 50 cc. After the alkaline mixture has been shaken for the two-hour period (Note 1) it is filtered, and the filtrate is acidified with 60 per cent sulfuric acid. If the acid is added slowly, the sulfinic acid comes down in fine crystals which after filtering and drying, melt at 155° with decomposition (Note 2). The yield is 50–55 g. (43–47 per cent of the theoretical amount based on the acetanilide used).

The product may be purified by crystallization from 400 cc. of hot water, but this is unnecessary when the above procedure is followed carefully.

2. Notes

1. The solution does not clear up when reduction is complete on account of the formation of a gelatinous impurity. Two hours suffice for the completion of reduction.

2. The melting point given in the literature (180°) is incorrect, its publication being due to a typographical error. The observed melting point varies slightly with the rate of heating during the determination of the melting point.

3. Other Methods of Preparation

p-Acetaminobenzene sulfinic acid has been prepared only by the reduction of *p*-acetaminobenzene sulfonyl chloride.[1]

[1] J. Chem. Soc. **125**, 2361 (1924).

II

p-ACETAMINOBENZENE SULFONYL CHLORIDE

$$C_6H_5NHCOCH_3 + 2HOSO_2Cl \rightarrow (p)\ CH_3CONHC_6H_4SO_2Cl + HCl + H_2SO_4$$

Submitted by S. Smiles and Jessie Stewart.
Checked by Henry Gilman and F. Schulze.

1. Procedure

In a 500 cc. round-bottom flask, fitted with a mechanical stirrer, is placed 290 g. (2.49 moles) of chlorosulfonic acid (Note 1). The flask is surrounded by a cooling bath and cooled with running water to about 12–15°. To the chlorosulfonic acid is added gradually 67.5 g. (0.5 moles) of acetanilide. This requires about fifteen minutes if the temperature is maintained at approximately 15°. Since large volumes of hydrogen chloride are evolved, the reaction should be conducted in a good hood. After all of the acetanilide has been added, the mixture is heated to 60° for two hours to complete the reaction (Note 2).

The syrupy liquid is poured slowly, with stirring (Note 3), into 1 kg. of ice to which just enough water has been added to make stirring easy. This decomposition of the excess chlorosulfonic acid should be carried out in the hood. The solid sulfonyl chloride which separates is collected on a suction funnel (Note 4) and washed with water. The yield of crude material is 90–95 g. (77–81 per cent of the theoretical amount based on the acetanilide).

This crude material may be used directly in many preparations such as *p*-acetaminobenzene sulfinic acid (p. 1). If a pure product is desired, the crude material is dried by pressing on a porous plate and then crystallized from dry benzene. The acid

chloride is slightly soluble in benzene and only 1.5 to 2 g. will dissolve in 100 cc. of hot benzene. On cooling, about 75 per cent of the material separates from the benzene in thick, colorless prisms melting at 149° (Note 5).

2. Notes

1. The chlorosulfonic acid should be freshly distilled. Smaller amounts of this reagent may be used without reducing the yield or affecting the quality of the product. However, with smaller amounts the time required for the reaction must be increased. Thus, if 175 g. of chlorosulfonic acid is used with 67.5 g. of acetanilide, an additional hour of heating is required to obtain the yields mentioned above.

2. The hydrogen chloride which is liberated during the reaction fills the mixture with tiny bubbles. When these disappear the reaction is complete.

3. Mechanical stirring is most convenient but not necessary.

4. A rather large suction funnel (125 mm. or more) should be used in the filtration as the sulfonyl chloride has a tendency to clog the filter.

5. The purification is the least satisfactory part of the preparation. The material must not be heated while water is still present, or excessive decomposition will occur. As the sulfonyl chloride is only slightly soluble in hot benzene, it is inconvenient to crystallize more than a small amount at a time. The crude product does not keep well and must be used at once. After recrystallization it may be kept indefinitely.

3. Other Methods of Preparation

p-Acetaminobenzene sulfonyl chloride has been prepared by the action of phosphorus pentachloride on sodium *p*-acetaminobenzene sulfonate[1] and by the action of chlorosulfonic acid on acetanilide.[2]

[1] Ber. **39**, 1563 (1906).
[2] J. Chem. Soc. **121**, 2558 (1922).

III

ACETONE DICARBOXYLIC ACID

$$CO_2HCH_2C(OH)(CO_2H)CH_2CO_2H + (\text{fuming } H_2SO_4) \rightarrow CO_2HCH_2COCH_2CO_2H + H_2O + CO$$

Submitted by ROGER ADAMS, H. M. CHILES, and C. F. RASSWEILER.
Checked by H. T. CLARKE and T. F. MURRAY.

1. Procedure

IN a 5-l. round-bottom flask (Note 1), fitted with an efficient mechanical stirrer, is placed 3000 g. of fuming sulfuric acid (20 per cent of free sulfur trioxide). Then the flask is cooled very efficiently with a thick pack of ice and salt, until the temperature of the acid registers $-5°$ (Note 2). The stirring is started, and 700 g. of finely powdered U. S. P. citric acid is added gradually. The speed of the addition is regulated according to the temperature of the reaction mixture. The temperature should not rise above 0° until half of the citric acid has been added, after which the temperature should not be allowed to exceed 10° until the reaction is complete. The addition requires three to four hours, provided efficient cooling is used. The citric acid should be in solution at the end of this time; if not, the stirring should be continued until it has dissolved completely.

The temperature of the reaction mixture is allowed to rise gradually until a vigorous evolution of gas commences; at this point the flask is cooled with ice water to stop the excessive frothing, but cooling is not carried far enough to stop the evolution of gas entirely (Note 3). After the more vigorous foaming has ceased, the reaction mixture is raised to about 30° and kept there until no more foaming occurs. A convenient way of determining this point is to stop the stirring for a moment and allow

the mixture to remain quiet. After a minute or so, a clear brown liquid giving off very few gas bubbles should result. This general procedure requires two to three hours.

The reaction mixture is cooled down again with ice and salt until the temperature reaches 0°, then 2400 g. of finely cracked ice is added in small portions at such a rate that the temperature does not rise above 10° until one-third of the ice has been added. Then the temperature may be allowed to rise to 25–30°. The addition of the ice requires about two hours; after this, the mixture is cooled again to 0° (Note 4) and then filtered as rapidly as possible through a funnel fitted with a filtros plate (Note 5). The crystals are thoroughly pressed and sucked as dry as possible. The acetone dicarboxylic acid is light gray to white in color. After the suction and pressing have removed practically all of the sulfuric acid, the crystals are transferred to a beaker and stirred with enough ethyl acetate (about 200 to 250 cc.) to make a thick paste. The crystals are filtered with suction. If acetone dicarboxylic acid entirely free from sulfuric acid is desired, the washing with ethyl acetate should be repeated. The yield of practically dry acetone dicarboxylic acid varies from 450–475 g. (92–97 per cent of the theoretical amount) (Note 6). This may be used directly for the preparation of the ester (p. 53). The acid itself is not stable and after a few hours gradually decomposes.

2. Notes

1. The reaction must be carried out in a good hood, since a large amount of carbon monoxide is liberated.

2. The use of a very efficient ice and salt mixture around the reaction flask is necessary if the reaction is to be carried out within the time indicated. It is very necessary to regulate the temperature as directed, since a considerably lower yield is obtained if the temperature rises.

3. Some cooling is necessary, or the rapid evolution of gas will cause the reaction mixture to foam over with consequent loss of material.

4. Vigorous cooling before final filtration of the acetone

dicarboxylic acid is essential to good yields, since the acid is fairly soluble in the reaction mixture.

5. The filtros plate for filtration can be very conveniently sealed into the Büchner funnel with a paste of water-glass and amorphous silica which is then hardened with concentrated sulfuric acid.

6. If the acid is to be esterified at once, careful drying from ethyl acetate is not necessary.

3. Other Methods of Preparation

Acetone dicarboxylic acid was first obtained by the action of concentrated sulfuric acid upon citric acid.[1] It has been made also by the gradual decomposition of a mixture of lime and sucrose.[2] The most satisfactory method, however, for producing this substance, is by the action of fuming sulfuric acid upon citric acid. Details of this preparation have been modified a number of times with the intention of improving the yield.[3]

The directions given in the above preparation are a slight modification of those given by Willstätter and Pfannenstiel.[4] While they are more complex than the details given by Ingold and Nickolls,[5] they give somewhat higher yields. The method of Ingold and Nickolls has been checked and has been found to have the advantage of requiring much less time.

[1] Ber. **17**, 2543 (1884).

[2] Ber. **26**, 3058 (1893).

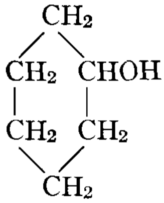
[3] Ann. **261**, 155 (1891); Gazz. chim. ital. **21**, I, 295 (1891); J. Chem. Soc. **75**, 809 Footnote (1889); **121**, 1642 (1922); Ann. **422**, 5 (1921).

[4] Ann. **422**, 5 (1921).

[5] J. Chem. Soc. **121**, 1642 (1922).

IV

ADIPIC ACID



$+4\ O(HNO_3) \rightarrow CO_2H(CH_2)_4CO_2H + H_2O$

Submitted by J. F. Thorpe and G. A. R. Kon.
Checked by Roger Adams, W. F. Tuley and C. R. Noller.

1. Procedure

A 3-l. three-necked round-bottom flask is fitted with a mechanical stirrer (Note 1), a dropping funnel, and a 90-cm. reflux water condenser carrying a tube to lead the oxides of nitrogen to a water trap or good hood. The stoppers should be made by cutting thin asbestos paper into strips about 2.5 cm. wide, moistening these in water-glass solution and then winding the strips around the end of the condenser until a stopper of the correct size is obtained. The apparatus is assembled and the stoppers are coated over with water-glass and allowed to harden over night (Note 2).

Twenty-seven hundred grams (29.9 moles) of concentrated nitric acid (sp. gr. 1.42) is placed in the flask and heated to boiling (Note 3). To the boiling solution, 500 g. (5 moles) of cyclohexanol (Note 4) is added through the separatory funnel at such a rate that it is all added in about five hours. The reaction is very vigorous at the beginning, and the cyclohexanol must be added at a rate of not more than 30 drops per minute. Toward the end, it may be added more rapidly. A large amount of oxides of nitrogen is given off during the oxidation. The reaction mix-

ture should be kept at the boiling point during the addition of the cyclohexanol and for ten to fifteen minutes longer in order to complete the reaction.

The reaction mixture is poured into a beaker and on cooling the adipic acid crystallizes. It is filtered with suction (Note 5), and the precipitate is washed once with about 200 cc. of cold water and dried in the air. The yield of slightly yellow adipic acid is 375–386 g. (55–56 per cent of the theoretical amount). This product is pure enough for most purposes. However, to remove the yellow color and obtain a purer product, this crude acid may be recrystallized from 700 cc. of concentrated nitric acid (sp. gr. 1.42). The loss in this purification is less than 10 per cent. The recrystallized acid melts at 153° (Notes 6 and 7).

2. Notes

1. If a mechanical stirring device is not available, the reaction may be carried out without stirring. A 5-l. flask should be used, and the mixture must be vigorously boiled to prevent the formation of a layer of cyclohexanol, which might lead to a violent reaction.

2. Corks may be used in assembling the apparatus, but they are badly attacked by the hot nitric acid and must be renewed with each run. The asbestos stoppers can be used repeatedly.

3. The nitric acid must be boiling hot, so that oxidation will set in as soon as the first drop of cyclohexanol is added. If any considerable amount of cyclohexanol is added before the oxidation starts, a serious explosion may result.

4. The cyclohexanol used was the commercial grade, which contains practically no phenol and of which 95 per cent boils between 158–163°.

5. The nitric acid mother liquors contain considerable amounts of adipic acid mixed with some glutaric acid and succinic acid. It is not practical to attempt to separate these acids by crystallization. However, by evaporating all of the nitric acid and then esterifying the resulting acid mixture with ethyl alcohol, a mixture of ethyl succinate (b. p. 121–126°/20 mm.),

ethyl glutarate (b. p. 133–138°/20 mm.), and ethyl adipate (b. p. 142–147°/20 mm.) can be obtained, from which considerable quantities of pure esters can be fractionated.

6. The nitric acid mother liquors from the purification of the first run may be used to recrystallize two or three subsequent batches of crude adipic acid, after which it may be employed as part of the acid for an oxidation.

7. Adipic acid may also be recrystallized from 2.5 times its weight of water or 50 per cent alcohol. However, the former solvent does not remove the yellow color and there is considerable loss in the mother liquors when the latter solvent is used.

3. Other Methods of Preparation

Adipic acid has been prepared by the following methods: the action of silver [1] or copper [2] on β-iodopropionic acid; the reduction of mucic acid with phosphorus and iodine; [3] the electrolysis of the potassium or sodium salts of monoethyl succinate; [4] the condensation of ethylene chloride or bromide with malonic ester or cyanoacetic ester and subsequent hydrolysis; [5] the oxidation of certain fractions of Baku petroleum; [6] the oxidation of cyclohexanol or cyclohexanone with nitric acid [7] or potassium permanganate.[8]

The method of Bouveault and Locquin,[9] which consists of oxidizing cyclohexanol with concentrated nitric acid, has been found to be the most useful for laboratory preparation.

[1] Ann. **149**, 221 (1869).

[2] J. Chem. Soc. **67**, 159 (1895).

[3] Ann. **125**, 20 (1863).

[4] Ann. **261**, 117 (1891); **347**, 40 (1906); Bull. soc. chim. (3) **29**, 1041 (1903).

[5] J. Chem. Soc. **65**, 578 (1894); **71**, 1063 (1897); **75**, 929 (1899); **95**, 699 (1909).

[6] Ann. **302**, 34 (1898); Ber. **32**, 1771 (1899).

[7] Rec. trav. chim. **24**, 23 (1905); Bull. soc. chim. (3) **34**, 208 (1905); (4) **3**, 438 (1908); Compt. rend. **168**, 1326 (1919).

[8] Ber. **39**, 2202 (1906); **41**, 575 (1908); **55B**, 3529 (1922); Bull. soc. chim. (4) **5**, 682 (1909).

[9] Bull. soc. chim. (4) **3**, 438 (1908).

V

BENZALANILINE

$$C_6H_5CHO + C_6H_5NH_2 \rightarrow C_6H_5CH{=}NC_6H_5 + H_2O$$

Submitted by Marston T. Bogert.
Checked by Henry Gilman and W. B. King.

1. Procedure

In a 500-cc. round-bottom flask are placed 93 g. (1 mole) of aniline and 106 g. (1 mole) of benzaldehyde (Note 1). The reaction mixture becomes quite warm and water distils. The flask is then heated in an oil bath so that the temperature of the contents is maintained at approximately 125° (Note 2) for about five hours, or until no more steam is evolved. The contents of the flask darken somewhat during the heating, but the material is homogeneous. Without cooling, the reaction mixture is slowly poured into iced water which is stirred constantly. The benzalaniline solidifies, and is filtered, washed twice with iced water, and sucked dry on the funnel. The crude wet material weighs 184–193 g. and melts at 48–50°.

The crude product, which contains considerable moisture, is purified by dissolving in boiling 95 per cent alcohol in a flask under a reflux condenser. Alcohol is added, a little at a time, until solution of the benzalaniline is complete; about 400 cc. is required. Water is then introduced into the boiling alcohol, a little at a time, until a permanent turbidity is obtained; about 150 cc. is required. The turbidity is removed by adding a few cubic centimeters of alcohol. The solution is then cooled rapidly with shaking or stirring, and the benzalaniline crystallizes (Note 3). It is filtered and then dried in the air. The yield is 154–157 g. (85–86 per cent of the theoretical amount) of a pro-

duct melting at 50–51°. By concentrating the filtrate to about 200 cc., an additional 15 g. melting at 47–50°, is obtained.

2. Notes

1. Both the aniline and the benzaldehyde should be freshly distilled in order to obtain the yields given in the procedure. In the distillation of the benzaldehyde, care must be taken or considerable oxidation will occur. Benzaldehyde distilled in the air contains about 0.5 per cent of benzoic acid.

2. The temperature of the reaction mixture does not exceed 110° until most of the water has been driven off.

3. Agitation is desirable during cooling, in order to prevent a brownish oil from settling to the bottom. This oil on solidification gives a dark-colored product. It is preferable to cool with iced-water.

3. Other Methods of Preparation

The only satisfactory method of preparing benzalaniline is the action of aniline on benzaldehyde.[1] The use of potassium pyrosulfate as a dehydrating agent, as suggested by Odell and Hines,[2] does not seem necessary.

[1] Jahresb. **1850**, 488.
[2] J. Am. Chem. Soc. **35**, 82 (1913).

VI

BENZALPINACOLONE

$$(CH_3)_3CCOCH_3 + C_6H_5CHO \rightarrow (CH_3)_3CCOCH = CHC_6H_5 + H_2O$$

Submitted by G. A. Hill and G. M. Bramann.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a 1500-cc. bottle are placed 100 g. (1 mole) of pinacolone (p. 91), 120 g. (1.13 moles) of freshly distilled benzaldehyde, 380 cc. of 95 per cent alcohol, 130 cc. of water, and 100 cc. of 10 per cent sodium hydroxide solution. The bottle is stoppered tightly, placed on a shaking machine, and agitated vigorously for about thirty-two hours (Note 1).

The reaction mixture is poured into a separatory funnel and diluted with an equal volume of water. The benzalpinacolone is separated by extracting three times with 300-cc. portions of benzene. The benzene extracts are combined and washed, first with water until the alkali is entirely removed, then with a saturated solution of sodium bisulfite, and finally two or three times with water. After drying over calcium chloride, the benzene is removed by distilling from a steam bath, and the residue is distilled under reduced pressure. The yield of distilled benzalpinacolone, boiling at 143–146°/10 mm. is 165–175 g. (88–93 per cent of the theoretical amount). This product is slightly yellow and melts at 41–42°. It is pure enough for most purposes. It may be recrystallized from 95 per cent alcohol and is then obtained in almost pure white crystals, melting at 43°.

2. Notes

1. The time may be shortened to twenty-four hours without greatly reducing the yield.

3. Other Methods of Preparation

Benzalpinacolone has been prepared only by the action of benzaldehyde on pinacolone in the presence of aqueous alcoholic alkalies. The method described above is a modification [1] of the original method devised by Vorländer and Kalkow.[2]

[1] J. Am. Chem. Soc. **45**, 1559 (1923).
[2] Ber. **30**, 2269 (1897).

VII

p-BROMOACETOPHENONE

$$C_6H_5Br + (CH_3CO)_2O + (AlCl_3) \rightarrow (p) BrC_6H_4COCH_3 + CH_3CO_2H$$

Submitted by ROGER ADAMS and C. R. NOLLER.
Checked by J. B. CONANT and C. R. KINNEY.

1. Procedure

IN a 5-l. round-bottom three-necked flask, fitted with a mechanical stirrer, separatory funnel, and reflux condenser holding a tube to carry off the evolved hydrogen chloride, is placed 392 g. (2.5 moles) of bromobenzene in 1-l. of dry carbon disulfide (Note 1). To this is added 750 g. (5.6 moles) (Note 2) of anhydrous aluminium chloride. The mixture is heated on a steam bath until gentle refluxing starts, and then 204 g. (2 moles) of acetic anhydride (Note 3) is added slowly through the dropping funnel. The time of addition is about one hour. Gentle refluxing should be continued throughout the time of addition of the anhydride and for an hour afterward. The reaction is accompanied by a copious evolution of hydrogen chloride which does not entirely cease even after this subsequent heating.

A condenser is attached to one of the side necks, and the carbon disulfide is distilled without removing the flask from the steam bath. After the removal of the solvent (Note 4), the reaction mixture is allowed to cool somewhat (Note 5); but while it is still warm, it is poured slowly with stirring over cracked ice to which hydrochloric acid has been added. In this way only a small amount of the aluminium chloride addition product remains in the flask. This is decomposed with ice and hydrochloric acid and added to the main product. The volume is now about 5 l. Each 2-l. portion is extracted twice with 300-cc.

and 200-cc. portions of benzene or ether. The extracts are combined and washed twice with water, once with 10 per cent sodium hydroxide solution, and twice more with water. The final water washings should be practically colorless and the separation sharp, allowing any precipitate to separate with the water. The extract is dried for an hour with about 30 g. of calcium chloride and filtered, and the solvent is distilled from a steam bath. Then the residue is distilled under reduced pressure with a short column (Org. Syn. **1**, 40). Some low-boiling material comes over first, and then the temperature rises rapidly. If care has been taken in the water decomposition to remove all of the aluminium salts (Note 6), the product comes over water-white and crystallizes to a white solid melting at 49–50.5°. The yield is 340–395 g. of a product boiling over a three-degree range (69–79 per cent of the theoretical amount). On redistillation the boiling point is 117°/7 mm.; 129–130°/15 mm.; and 255.5°/736 mm.

2. Notes

1. If the carbon disulfide-bromobenzene solution is not clear it should be dried over calcium chloride and filtered before the aluminium chloride is added. In using such large amounts of carbon disulfide, particular precautions must be taken to prevent fires.

2. The aluminium chloride should be added in about this excess. When the excess is larger the yield does not seem to be increased, and when only 2 equivalents are used it is diminished by 10 to 15 per cent.

3. The acetic anhydride should boil at 136–139°. Some commercial grades are satisfactory, whereas others have been found to contain almost 50 per cent of acetic acid.

4. About 600 to 800 cc. of carbon disulfide is recovered and may be used in the next run.

5. If the product is allowed to come to room temperature before decomposition with water, it becomes semi-solid and is not easily removed from the flask.

6. If the aluminium chloride double compound is not entirely

decomposed by water and the aluminium salts thus removed, the distillate comes over slightly red and does not crystallize well on cooling. Redistillation, however, gives a pure product.

7. This method is an improvement over the older methods for the preparation of substituted acetophenone derivatives. The yields obtained by the use of acetyl chloride in place of acetic anhydride in the preparation of *p*-bromoacetophenone were invariably lower.

8. Under the same general conditions, satisfactory yields of other acetophenones may be obtained. Thus, from 281 g. of chlorobenzene, 750 g. of aluminium chloride, and 205 g. of acetic anhydride, a consistent yield of 285 to 300 g. (70–73 per cent of the theoretical amount) of *p*-chloroacetophenone, boiling at 124–126°/24 mm. and melting at 20–21°, is obtained. Similarly, acetophenone may be obtained in 76–83 per cent yields, *p*-methylacetophenone in 85–89 per cent yields, and *p*-methoxyacetophenone in 90–94 per cent yields.

3. Other Methods of Preparation

p-Bromoacetophenone has been made by the action of acetyl chloride in carbon disulfide on bromobenzene in the presence of anhydrous aluminium chloride,[1] and by the use of acetic anhydride in place of the acetyl chloride.[2]

[1] Ber. **24**, 550, 3766 (1891); J. Am. Chem. Soc. **35**, 266 (1913).
[2] J. Am. Chem. Soc. **46**, 1892 (1924).

VIII

p-BROMOTOLUENE

$$(p)\ CH_3C_6H_4NH_2 + HNO_2 + H_2SO_4 \rightarrow (p)\ CH_3C_6H_4N_2SO_4H + 2H_2O$$

$$(p)\ CH_3C_6H_4N_2SO_4H + HBr + (CuBr) \rightarrow (p)\ CH_3C_6H_4Br + N_2 + H_2SO_4$$

Submitted by LUCIUS A. BIGELOW.
Checked by C. S. MARVEL and A. E. BRODERICK.

1. Procedure

A MIXTURE of 63 g. (0.25 mole) of crystallized cupric sulfate, 20 g. (0.31 mole) of copper turnings, 154 g. (1.1 moles) of sodium bromide, 30 g. (0.28 mole) of concentrated sulfuric acid (sp. gr. 1.84), and 1 l. of water is refluxed over a flame for three to four hours until the color becomes yellowish (Note 1).

When the hydrobromic acid-cuprous bromide solution is ready for use, the diazonium solution is prepared. A solution of 107 g. (1 mole) of *p*-toluidine and 196 g. (1.9 moles) of concentrated sulfuric acid (sp. gr. 1.84) in 1 l. of water is cooled below 20° and diazotized with a solution of 70 g. (1 mole) of sodium nitrite in 125 cc. of water. This requires about twenty to thirty minutes when the temperature is maintained between 15° and 20° by means of an ice bath.

A 5-l. round-bottom flask containing the hydrobromic acid-cuprous bromide solution, is arranged for steam distillation. After the copper solution is heated to boiling, the diazonium solution is gradually added from a separatory funnel and a vigorous current of steam is passed through the reaction mixture at the same time. This procedure requires about two hours.

The aqueous distillate is made alkaline with sodium hydroxide solution and the *p*-bromotoluene is separated from the water layer (Note 2). The crude product weighs 131–137 g. For purification the crude product is washed once with concentrated sulfuric acid (Note 3) and then with water. It is dried over a little calcium chloride, filtered, and distilled. The yield of pure product amounts to 120–126 g. (70–73 per cent of the theoretical amount) boiling at 183–185° and melting at 25–26°.

2. Notes

1. If the color of the solution has not been discharged after heating for three to four hours, a few grams of sodium sulfite may be added to complete the reduction.

2. A small amount of ether or benzene may be used to aid in the separation if it is needed.

3. The sulfuric acid treatment is necessary if a colorless product is to be obtained. If ether is used in the extraction of the *p*-bromotoluene, it must be removed before washing with sulfuric acid.

3. Other Methods of Preparation

p-Bromotoluene has been obtained by the bromination of toluene with bromine in the presence of various catalysts [1] and with hypobromous acid.[2] The best method for its preparation, however, is the diazotization of *p*-toluidine followed by replacement of the diazonium group by bromine.[3]

[1] Ann. **136**, 301 (1865); **154**, 294 (1870); **242**, 165 (1887); Z. Chem. **1869**, 138; Ber. **18**, 608 (1885); Compt. rend. **158**, 1806 (1914).

[2] Ber. **43**, 673 (1910).

[3] Ber. **37**, 994 (1904).

IX

n-BUTYL *n*-BUTYRATE

$$6C_4H_9OH + 2Na_2Cr_2O_7 + 8H_2SO_4 \rightarrow 3C_3H_7CO_2C_4H_9 + 2Cr_2(SO_4)_3 + 2Na_2SO_4 + 14H_2O$$

Submitted by G. Ross Robertson.
Checked by Henry Gilman and J. E. Kirby.

1. Procedure

In a 2-l. flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel, are placed a cool solution of 240 cc. (4.3 moles) of commercial sulfuric acid (sp. gr. 1.84) in 240 cc. of water, and 240 g. (3.21 moles) of technical *n*-butyl alcohol (Note 1). The whole is placed in a large, efficient ice-salt bath.

A solution of 320 g. (1.07 moles) of crystalline sodium dichromate (350 g. of the ordinary moist technical hydrated salt is also suitable) in 200 cc. of water is dropped from the funnel into the vigorously stirred alcohol mixture as rapidly as can be done without running the temperature above 20°. When most of the dichromate has been added, the viscosity of the reaction mixture becomes so great that the stirring is rendered inefficient. The temperature is now allowed to rise to 35° if necessary (Note 2), to accelerate the reaction.

The resulting green syrupy emulsion is diluted with an equal volume of water, whereupon 220–225 cc. of an oil containing the desired ester (Note 3), slowly separates. This oil is washed three times with water, separated, and treated with a few grams of anhydrous sodium sulfate in order to remove most of the water. It is now distilled slowly through a large, efficient fractionating column. The fraction boiling at 150–170° is collected, and should amount to 170–175 cc. It is washed with

five 15-cc. portions of 60 per cent sulfuric acid (sp. gr. about 1.5) (Note 4), is then washed free of acids with dilute sodium hydroxide, and finally washed free of alkali with cold water. It is rapidily dried, as before, with sodium sulfate, and fractionated through the same distilling column. The fraction boiling at 162–166° (uncorr.) consists of *n*-butyl *n*-butyrate, containing a small percentage of residual butyl alcohol. The yield is 96–110 g. (41–47 per cent of the theoretical amount).

If higher purity is desired, the fractionation must be repeated. An additional yield may be secured by further fractionation of the lower-boiling fractions (Note 5).

2. Notes

1. When *n*-butyl alcohol is oxidized to butyric acid in the presence of a high concentration of sulfuric acid, esterification takes place at once, even in the cold, as long as an excess of the alcohol is present.

2. If the temperature of the reaction mixture is allowed to rise much above 35°, considerable material escapes in the form of butyraldehyde (b. p. 74°).

3. The oil obtained as the first crude product contains, in addition to the desired ester, much unchanged butyl alcohol, a little butyraldehyde, and a little free butyric acid.

4. The 60 per cent sulfuric acid is chosen as a wash liquid because it is miscible with butyl alcohol but not with the ester. The volatile aldehyde disappears in the two fractionations, while the butyric acid is removed by the alkali.

5. The low-boiling fractions could no doubt be returned to a new batch if this process were carried out repeatedly in quantity production. About 25 per cent of the original butyl alcohol can be recovered if desired. The very small fractions boiling above 166° may contain esters of other alcohols occurring in the technical product used, and possibly butyl succinate and related by-products.

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3. Other Methods of Preparation

n-Butyl *n*-butyrate has been made by the interaction of *n*-butyl alcohol and *n*-butyric acid in the presence of sulfuric acid,[1] and by the action of *n*-butyl iodide on silver *n*-butyrate.[2]

[1] Ann. **233**, 269 (1886).
[2] Ann. **158**, 170 (1871).

X

n-BUTYL CHLORIDE

$$CH_3(CH_2)_2CH_2OH + HCl + (ZnCl_2) \rightarrow CH_3(CH_2)_2CH_2Cl + H_2O$$

Submitted by J. F. NORRIS.
Checked by C. S. MARVEL and W. D. LANSING.

1. Procedure

To 190 g. (2 moles) of cold concentrated hydrochloric acid (sp. gr. 1.19) is added 272 g. (2 moles) of anhydrous zinc chloride. The mixture is kept cold to avoid loss of hydrogen chloride. To this solution, 74 g. of *n*-butyl alcohol (1 mole) is added (Note 1). The mixture is then refluxed over a free flame for three and one-half to four hours (Note 2). After cooling, the upper layer is separated (Note 3) and placed in a distilling flask with an equal volume of concentrated sulfuric acid (Note 4). The side arm of the flask is closed and the neck is connected with a reflux condenser. After refluxing gently for one-half hour, the chloride is distilled. The distillate is washed with water, dried over calcium chloride, filtered, and distilled. The fraction boiling at 76–78° weighs 59–61 g. (64–66 per cent of the theoretical amount).

2. Notes

1. The best results were obtained when the substances were used in the molecular ratio: 1 of alcohol, 2 of hydrogen chloride as concentrated hydrochloric acid, and 2 of zinc chloride.

2. Shorter periods of heating diminish the yields. Heating on a steam bath also gives lower yields. The mixture should be boiled rather vigorously over a flame. With larger runs, an even longer heating period must be used. It is necessary to boil a

5-mole alcohol run for nine hours to obtain the yield mentioned in the procedure.

3. The zinc chloride may be recovered from the aqueous solution by evaporation until a syrupy residue is obtained. This may be used in the next run.

4. This treatment with sulfuric acid is carried out in order to remove high-boiling impurities that are not easily separated by fractional distillation.

5. Other alkyl chlorides may be prepared by this general procedure.[12] The following yields are obtained with some of the common alcohols, used in the molecular proportions given under the procedure: *n*-propyl chloride, 55–61 per cent; iso-propyl chloride, 70–76 per cent; *sec.*-butyl chloride, 60–65 per cent; 2-chloropentane, 60–70 per cent.

3. Other Methods of Preparation

Alkyl chlorides have been obtained by the direct chlorination of hydrocarbons [1] and by the addition of hydrogen chloride to olefines.[2] However, they have usually been prepared from the corresponding alcohol by the action of a number of reagents, such as dry hydrogen chloride,[3] dry hydrogen chloride in the presence of zinc chloride,[4] phosphorus trichloride,[5] phosphorus oxychloride,[6] phosphorus pentachloride,[7] phosphorus trichloride

[1] Ann. chim. phys. (3) **52**, 98 (1858); Jahresb. **1863**, 524; Ann. **131**, 76 (1864); **132**, 234 (1864); **144**, 186 (1867); **150**, 210 (1869); **152**, 159 (1869); **161**, 265 (1871); Am. Chem. J. **19**, 245 (1897); Ber. **31**, 1802 (1898); J. prakt. Chem. (2) **59**, 562 (1899).

[2] Ann. **127**, 71 (1863); **189**, 51 (1877); **196**, 124 (1879); Ann. chim. phys. (4) **3**, 161 (1864); U. S. Pat. 1,518,182; Chem. Zentr. **1925**, I, 1129.

[3] Ann. **52**, 312 (1844); **152**, 5 (1869); **158**, 160 (1871); **159**, 72 (1871); **189**, 3 (1877); **190**, 312 (1878); **351**, 188 (1907); Z. Chem. **1871**, 147; Bull. soc. chim. (3) **1**, 603 (1889); (3) **2**, 136 (1889); (3) **25**, 844 (1901); Monatsh. **28**, 559 (1907); U. S. Pat. 1,440,683; C. A. **17**, 1029 (1923).

[4] Ann. **174**, 372 (1874); Ber. **7**, 741 (1874); J. prakt. Chem. (2) **14**, 196 (1876); Ann. chim. phys. (6) **19**, 406 (1890); U. S. Pat. 1,509,463; Chem. Zentr. **1925** I, 573.

[5] J. Russ. Phys. Chem. Soc. **29**, 223 (1897); Chem. Zentr. **1897**, II, 334; J. Chem. Soc. **87**, 1594 (1905).

[6] Ann. **102**, 334 (1857); Ber. **6**, 35 (1873).

[7] Ann. **37**, 164 (1841); **92**, 398 (1854); **103**, 81 (1857); **163**, 266 (1872); **177**, 183 (1875); **179**, 321 (1875); **183**, 348 (1876); **190**, 336 (1878); **191**, 131 (1878).

in the presence of zinc chloride,[8] sodium chloride and sulfuric acid,[9] aqueous hydrochloric acid,[10] and aqueous hydrochloric acid in the presence of calcium chloride.[11] The method above described is more convenient than the older methods using anhydrous hydrogen chloride, and better yields are obtained than can be had by the use of aqueous hydrochloric acid with other catalysts.[12]

[8] J. Am. Chem. Soc. **29**, 1328 (1907).

[9] Ann. **15**, 17 (1835).

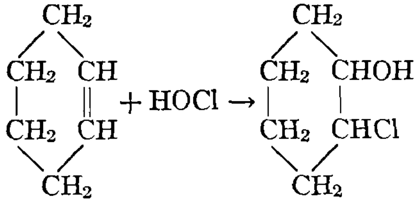
[10] Am. Chem. J. **38**, 641 (1907); J. Am. Chem. Soc. **38**, 1071 (1916); **42**, 2093 (1920).

[11] Ger. Pat. 280,740; Frdl. **12**, 22 (1914).

[12] J. Am. Chem. Soc. **46**, 753 (1924).

XI

o-CHLOROCYCLOHEXANOL



Submitted by G. H. Coleman and H. F. Johnstone.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

To a solution of 25 g. of mercuric chloride in 500 cc. of water in a 5-l. flask, 800 g. of cracked ice is added. A cold solution of 190 g. of sodium hydroxide in 500 cc. of water is added, and a rapid stream of chlorine is passed into the mixture, which must be kept below 5°. The addition of chlorine is continued in this way until the yellow precipitate of mercuric oxide just disappears. Then 600 cc. of cold nitric acid (1.5 N) is added slowly, with stirring.

The concentration of the hypochlorous acid solution is determined by adding a measured volume to an excess of potassium iodide solution acidified with hydrochloric acid, and titrating with standard thiosulfate solution. Usually the concentration is found to be between 3.5 and 4 per cent. The amount necessary to react with 123 g. (1.5 moles) of cyclohexene is calculated.

In a 5-l. round-bottom flask equipped with a good mechanical stirrer (Note 1), is placed 123 g. (1.5 moles) of cyclohexene (p. 33), and to it is added about one-fourth the calculated amount of the hypochlorous acid solution. The mixture is kept below 15° and stirred vigorously until a 1-cc. test portion gives no yellow

color when it is treated with potassium iodide solution and dilute hydrochloric acid. When the first portion of the hypochlorous acid has reacted, a second is added and the process is repeated. When all the hypochlorous acid has been added and the reaction is complete, the oily layer should be on the bottom and a very slight excess of hypochlorous acid should be present, as indicated by the potassium iodide test. If these conditions are not fulfilled, 100-cc. portions of the hypochlorous acid solution are added until the reaction is shown to be complete.

The solution is now saturated with salt and distilled with steam (Note 2). About 2 l. of distillate is required before all of the *o*-chlorocyclohexanol passes over. The distillate is saturated with salt and the oily layer separated. The aqueous layer is extracted once with about 250 cc. of ether. This is added to the main portion, which is dried with anhydrous sodium sulfate. The ether is removed by distillation and the product distilled under reduced pressure. The fraction boiling between 88–90°/20 mm. (104–106°/45 mm.) is collected. The yield is 142–148 g. (70–73 per cent of the theoretical amount).

2. Notes

1. If a mechanical stirrer is not available, shaking the flask by hand will give as good results.

2. In the separation of the product from the hypochlorous acid solution, steam distillation seems to be desirable. In several runs in which this was not carried out, a larger amount of a dark-colored high-boiling residue remained in the flask after distillation, and the yield of *o*-chlorocyclohexanol was smaller.

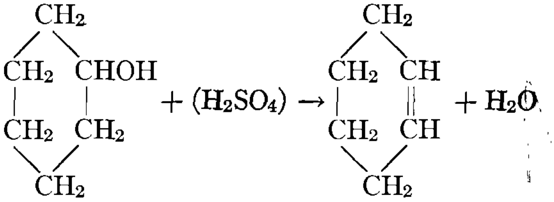
3. Other Methods of Preparation

o-Chlorocyclohexanol has been prepared only by the action of hypochlorous acid on cyclohexene.[1] The methods that have been given in the literature differ mainly in the manner in which the hypochlorous acid is obtained. The yields are practically the same by all of the procedures.

[1] J. Chem. Soc. **73**, 948 (1898); J. Am. Chem. Soc. **42**, 2621 (1920); Bull. soc. chim. (4) **31**, 177 (1922).

XII

CYCLOHEXENE



Submitted by G. H. Coleman and H. F. Johnstone.
Checked by C. S. Marvel and A. B. Adams.

1. Proceaure

In a 500-cc. modified Claisen flask (Org. Syn. 1, 40) are placed *400 g. of cyclohexanol* (*Note 1*) *and 12 cc. of concentrated sulfuric acid*, and the flask is connected to a condenser and receiver. It is then placed in an oil bath which is heated to a temperature of 130–140°. The distillation is continued until only a small residue remains and the odor of sulfur dioxide is apparent. Toward the end of the distillation the temperature of the bath may be raised to 150°. The receiver is surrounded with an ice bath (Note 2) during the entire distillation which requires from five to six hours.

The distillate is saturated with salt, and the cyclohexene is separated from the water layer. It is dried with calcium chloride and fractionated through an efficient column. The fraction boiling at 80–82° (uncorr.) is collected separately. It may be necessary to refractionate the low- and high-boiling portions once or twice. The high-boiling fraction is finally added to the next run. The yield of cyclohexene is 260–285 g. (78–87 per cent of the theoretical amount.)

2. Notes

1. The ordinary commercial grade of cyclohexanol was used in these experiments. It contained no more than a trace of phenol and 90–95 per cent of it distilled at 158–163°.

2. In transferring cyclohexene, it is best to keep it well cooled to avoid small losses by evaporation.

3. Other Methods of Preparation

The practical method of preparing cyclohexene is the dehydration of cyclohexanol. Many reagents have been used for this purpose. The following is a partial list: potassium bisulfate,[1] oxalic acid,[2] sulfuric acid,[3] *p*-toluene sulfonic acid,[4] and iodine.[5] In addition, cyclohexanol has been dehydrated at high temperatures over various catalysts.[6]

The method described in the procedure is a slight modification of one that was first devised by Senderens [7] and later modified by Kendall and Osterberg.[8]

[1] Bull. soc. chim. (3) **33**, 270 (1905); Ber. **45**, 1466 (1912).

[2] Ber. **34**, 3252 (1901); **45**, 1466 (1912); J. Russ. Phys. Chem. Soc. **43**, 1222 (1911); Chem. Zentr. **1912**, I, 139; Bull. soc. chim. (4) **17**, 174 (1915).

[3] Compt. rend. **154**, 1169 (1912); J. Am. Chem. Soc. **42**, 2620 (1920).

[4] Bull. soc. chim. Belg. **26**, 304 (1912); Chem. Zentr. **1912**, II, 1006.

[5] J. Am. Chem. Soc. **37**, 1754 (1915).

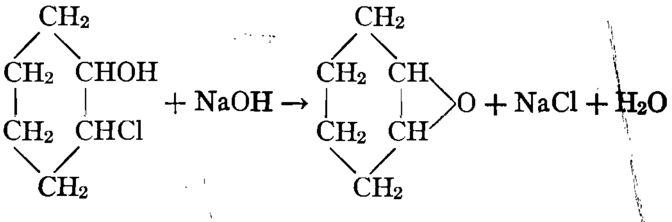
[6] Ber. **43**, 3385 (1910); Ger. Pat. 241,895; Frdl. **10**, 1032 (1911); Ann. chim. phys. (8) **25**, 461, 500 (1912).

[7] Compt. rend. **154**, 1169 (1912).

[8] J. Am. Chem. Soc. **42**, 2620 (1920).

XIII

CYCLOHEXENE OXIDE



Submitted by A. E. Osterberg.
Checked by C. S. Marvel and A. B. Adams.

1. Procedure

In a 2-l. round-bottom flask fitted with a mechanical stirrer, is placed a solution of 70 g. (1.75 moles) of sodium hydroxide in 400 cc. of water. To this solution is then added 230 g. (1.71 moles) of *o*-chlorocyclohexanol (p. 31). The mixture is stirred vigorously for about one hour (Note 1). The stirring is then stopped and the upper layer is separated and fractionated carefully through an efficient column.

The fractions collected are 100–129°, 129–134°, and 134–175° (Note 2). The first fraction is mainly cyclohexene oxide but contains some water which is separated with a separatory funnel before the second fractionation. After the fraction boiling at 100–129° is collected, the condenser should be removed and dried thoroughly before collecting the second fraction, in order to insure anhydrous material. After two or three fractionations, the yield of cyclohexene oxide boiling at 129–134° is 117–122 g. (70–73 per cent of the theoretical amount).

2. Notes

1. If the stirring is continued for much longer than one and one-half hours, the yield may be lessened somewhat.

2. There is a slight high-boiling residue which begins to decompose if the temperature is raised above this point. The products of decomposition are hard to remove from the distilling flask.

3. Other Methods of Preparation

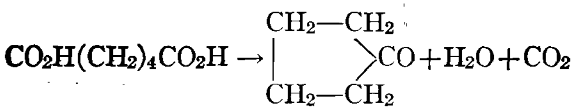
Cyclohexene oxide was first prepared by Brunel from *o*-iodocyclohexanol and solid potassium hydroxide.[1] It has also been obtained by the oxidation of cyclohexene with benzoyl hydroperoxide.[2]

[1] Compt. rend. **136**, 384 (1903); **137**, 62 (1903); Bull. soc. chim. (3) **29**, 883 (1903).

[2] Compt. rend. **174**, 462 (1922).

XIV

CYCLOPENTANONE



Submitted by J. F. Thorpe and G. A. R. Kon.
Checked by Roger Adams and C. R. Noller.

1. Procedure

In a 1-l. distilling flask (Note 1) fitted with a thermometer reaching within 5 mm. of the bottom, is placed an intimate mixture of 200 g. of powdered adipic acid (Note 2) and 10 g. of finely ground crystallized barium hydroxide. The mixture is gradually heated in a fusible alloy bath (Note 3) to 285–295° (Note 4) during about one and one-half hours, and maintained at that temperature until only a small amount of dry residue remains in the flask. This requires about two hours longer. The cyclopentanone distils slowly, accompanied by small quantities of adipic acid.

The ketone is separated from the water in the distillate, either by salting out with calcium chloride or by extraction with a little ether. It is washed with a little aqueous alkali and then with water, dried over calcium chloride, and distilled through a good fractionating column (Note 5). The fraction boiling at 128–131° is cyclopentanone. The yield is 86–92 g. (75–80 per cent of the theoretical amount).

2. Notes

1. If larger runs are made, a three-neck flask provided with a mechanical stirrer should be used for the reaction.

2. The unrecrystallized adipic acid, prepared as described on page 9, may be used.

3. An air bath may be used, but the metal bath insures better temperature control.

4. If the temperature goes above 300°, the adipic acid begins to distil quite rapidly. It is best to hold the temperature as near 290° as is possible.

5. Cyclopentanone is quite volatile with ether vapor, and careful fractionation is necessary when ether is used for the separation of the ketone from the water.

3. Other Methods of Preparation

Cyclopentanone has been prepared from adipic acid by distilling the calcium salt,[1] heating alone [2] or with acetic anhydride,[3] or in the presence of various catalysts such as barium hydroxide,[4] thorium oxide,[5] manganous oxide,[5] uranium nitrate,[6] ferrous sulfate [6] and others.[7]

[1] Ann. **275**, 312 (1893); Rec. trav. chim. **24**, 23 (1905).
[2] Ber. **45**, 1605 (1912).
[3] Compt. rend. **144**, 1357 (1907); Ann. chim. phys. (8) **26**, 43 (1912).
[4] Ger. Pat. 256,622; Frdl. **11**, 49 (1913); Ann. **410**, 36 (1915).
[5] Compt. rend. **158**, 987 (1914).
[6] Ger. Pat. 256,622; Frdl. **11**, 49 (1913).
[7] Compt. rend. **168**, 1326 (1919).

XV

l-CYSTINE

Hydrolysis of Keratin from Hair ⟶

$CO_2HCH(NH_2)CH_2SSCH_2CH(NH_2)CO_2H$

Submitted by R. A. Gortner and W. F. Hoffman.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

Human hair (Note 1) is freed from foreign matter (Note 2), washed well with a lukewarm solution of soap (Note 3), then twice with cold distilled water, and dried. This washing removes the natural oils from the hair (Note 4). Two kilos of the dry, washed hair is pushed into a 12-l. round-bottom Pyrex flask, and 4 l. of 20 per cent hydrochloric acid (Note 5) is added. An air-cooled reflux condenser, consisting of a wide glass tube, is attached to the flask. The hair is hydrolyzed by heating on the steam bath (Note 6) until the biuret reaction is entirely negative; this requires one hundred twenty to one hundred forty-four hours.

The mixture is filtered hot and the insoluble residue is washed with distilled water. The total filtrate is now partially neutralized with 300 cc. of 40 per cent sodium hydroxide solution, while the mixture is well stirred and cooled, and then a saturated solution of 3750 g. of crystallized sodium acetate is added. The Congo Red test for mineral acid should then be entirely negative. Care must be taken *not to make the solution alkaline* with sodium hydroxide (Note 7). After standing for three days at room temperature, the precipitated cystine is filtered on a suction funnel. This crude material, containing in addition to the

cystine, some "humin," pigments, and tyrosine, is dissolved in 3 l. of 3 per cent hydrochloric acid. The solution is filtered and competely decolorized by two to five treatments with 20–25 g. portions of decolorizing carbon (Norit) which has been completely freed from calcium phosphate by boiling with dilute hydrochloric acid and washing with cold water. The filtrate after decolorizing should be water-clear, or at the most only slightly yellow. If it shows more color, the treatment with decolorizing carbon should be carried out again. The solution should finally be filtered once by gravity to remove traces of a solid impurity which is apt to pass through the suction funnel. The cystine is precipitated from the clear solution by adding a filtered saturated solution of 900–1000 g. of crystallized sodium acetate until the Congo Red reaction is negative. After standing five to six hours (Note 8), the cystine is filtered and washed twice with 100–200 cc. portions of hot, distilled water to remove the last traces of tyrosine. By this method the typical colorless hexagonal plates of cystine are obtained. The yield is 100–106 g. (5.0–5.3 per cent of the weight of the starting material).

2. Notes

1. Crude sheep's wool may also be employed, but the yield is not so high (about 2.6 per cent).

2. Hair obtained from barber shops generally contains matches, paper, cigar and cigarette butts, and similar impurities which should be sorted out by hand as completely as possible. The other principal contamination is sand which causes little trouble and need not be removed.

3. A high grade of soap should be employed. Hair kept in hot dilute sodium carbonate solution for one to two hours yields little or no cystine.

4. The oily material may also be removed by extracting with gasoline or benzene, but this procedure involves considerably more labor.

5. The constant-boiling (20 per cent) hydrochloric acid may be prepared by adding 2000 cc. of water to 2700 cc. of concentrated hydrochloric acid (sp. gr. 1.20).

6. The hydrolysis can be carried out in a much shorter time by heating over a flame or on a sand bath, but there is great danger of breaking the flask on account of bumping.

7. An alkaline reaction must always be avoided, as even dilute sodium carbonate decomposes cystine.

8. If the mixture is allowed to stand for a longer time, tyrosine tends to crystallize out with the cystine.

3. Other Methods of Preparation

l-Cystine has been obtained by the hydrolysis of a large number of proteins. However, the keratins are the only common proteins rich enough in cystine to serve as a source for this amino acid. Many investigators have devised methods for its isolation from the hydrolytic products of human hair,[1] wool,[2] horn,[3] nail,[3] feathers,[3] and horse hair.[4] The method of Folin[5] is the basis for most of the others. The present method does not claim to give as high a yield as some of those reported in the literature, but is convenient and gives consistent results.

[1] Z. physiol. Chem. **34**, 225 (1902); **52**, 475 (1907); Beitr. Chem. Physiol. Path. **3**, 16 (1903); J. Biol. Chem. **9**, 369 (1911); **55**, 671 (1923); J. prakt. Chem. (2) **95**, 360 (1917); J. Am. Chem. Soc. **44**, 346 (1922); C. A. **17**, 293 (1923).

[2] Z. physiol. Chem. **52**, 360 (1907); J. Biol Chem. **8**, 10 (1910); J. Am. Chem. Soc. **43**, 2692 (1921); **44**, 346 (1922); C. A. **17**, 293 (1923).

[3] Z. physiol. Chem. **28**, 599 (1899); **32**, 97 (1901); **34**, 218 (1902); **52**, 367, 479 (1907); **69**, 310 (1910); Beitr. Chem. Physiol. Path. **3**, 15 (1903); J. Biol. Chem. **9**, 369 (1911).

[4] Z. physiol. Chem. **39**, 352 (1903); Fischer, Anleitung zur Darstellung org. Präp. 9th Ed. page 93.

[5] J. Biol. Chem. **8**, 10 (1910).

XVI

DIALLYL AMINE

$$(CH_2{=}CHCH_2)_2NCN + 2H_2O \rightarrow (CH_2{=}CHCH_2)_2NH + NH_3 + CO_2$$

Submitted by E. B. Vliet.
Checked by Roger Adams and E. E. Dreger.

1. Procedure

A solution of 123 g. (1.2 moles) of sulfuric acid (sp. gr. 1.84) in 370 cc. of water is placed in a 2-l. round-bottom flask equipped with a reflux condenser. To this is added 98.5 g. (0.8 mole) of diallyl cyanamide (p. 45) and a few pieces of clay plate to prevent bumping. The mixture is refluxed gently for six hours. During the first fifteen minutes of heating, some bumping occurs. However, the mixture gradually becomes homogeneous and the boiling then proceeds smoothly (Note 1).

After six hours, the solution is cooled to room temperature and a cold solution of 192 g. (4.8 moles) of sodium hydroxide in 350 cc. of water is poured down the side of the flask so that most of it settles to the bottom without mixing with the solution in the flask. The flask is then connected to a condenser for downward distillation and is shaken to mix the two layers. The resulting free amine separates. The flask is heated and the amine, together with some water, distils. The distillation is continued until no amine separates from a test portion of the distillate. There is a small quantity of an oily liquid left floating in the flask. This is probably an impurity from the diallyl cyanamide.

The weight of water in the distillate is estimated, and about one-half of this amount of potassium hydroxide is added in the form of sticks, so that it will dissolve slowly. The mixture should

be kept cool while the potassium hydroxide is dissolving. Bubbles of ammonia gas will be evolved. When solution of the potassium hydroxide is complete, the amine is separated and dried for several hours over solid sodium hydroxide which has been freshly broken up into small lumps. It is then filtered into a distilling flask and distilled at atmospheric pressure. If the product has been thoroughly dried, there should be no low-boiling material. All of the diallyl amine should come over at 108–111° and only a very small amount of higher-boiling material should remain. The yield is 62–68 g. (80–86 per cent of the theoretical amount).

2. Notes

1. Alkali may be used for this hydrolysis instead of acid; but it is not as satisfactory, since the reaction mixture remains in two layers, thus causing the hydrolysis to proceed more slowly. Furthermore, any slight leak in the apparatus during refluxing permits a loss of product.

2. This reaction represents a general method for the preparation of secondary amines; thus, di-*n*-butyl amine has been obtained from di-*n*-butyl cyanamide in yields of 75 per cent of the theoretical amount.

3. Other Methods of Preparation

Diallyl amine has been prepared from allyl amine and allyl bromide,[1] and from allyl amine and allyl chloride.[2] Experiments on these methods showed that the resulting product contained relatively large amounts of triallyl amine and monoallyl amine and it was very difficult to isolate pure diallyl amine. The above synthesis from diallyl cyanamide, which has recently appeared in the literature,[3] is more satisfactory than the older methods.

[1] Ber. **14**, 1879 (1881).

[2] Ber. **16**, 1641 (1883).

[3] J. Am. Chem. Soc. **46**, 1307 (1924); Versuche mit Diallylderivaten, Dissertation von Paul Graf, Eidgenossischen Technischen Hochschule, Zurich; page 29.

XVII

DIALLYL CYANAMIDE

$$CaNCN + 2NaOH \rightarrow Ca(OH)_2 + Na_2NCN$$

$$Na_2NCN + 2CH_2{=}CHCH_2Br \rightarrow (CH_2{=}CHCH_2)_2NCN + 2NaBr$$

Submitted by E. B. Vliet.
Checked by Roger Adams and E. E. Dreger.

1. Procedure

In a 5-l. round-bottom two-necked flask, fitted with a reflux condenser and a mechanical stirrer with a mercury seal, are placed 660 cc. of cold water and 135 g. of cracked ice. Two hundred grams (containing about 1.4 moles of pure calcium cyanamide) of fresh lime nitrogen (Note 1) is added slowly, with stirring. As soon as the lime nitrogen is suspended thoroughly in the water, a cold solution of 110 g. (2.75 moles) of sodium hydroxide in 200 cc. of water is added slowly, with stirring. Then the suspension is stirred quite briskly during one hour. If the temperature rises above 25°, small amounts of ice should be added (Note 2).

To the solution of sodium cyanamide thus prepared, 380 g. (3.14 moles) of allyl bromide (Note 3) and 660 cc. of 95 per cent alcohol are added. The mixture is then heated on a water bath with good stirring until it refluxes gently, and the heating and stirring are continued for two and one-half hours. Then the reflux condenser is replaced by one set downward for distillation. The stirring is continued and the alcohol is distilled until about 500 cc. has been collected. The distillate may be discarded or used for the recovery of alcohol (Note 4).

The reaction mixture is cooled to room temperature and filtered with suction through a large Büchner funnel. The residue

is washed with alcohol. The filtrate which will be in two layers, is extracted twice with benzene first with 270 cc. and then with 130 cc. The combined benzene extracts are dried with sodium sulphate and then filtered into a distilling flask. The benzene is distilled from a water bath, and then the diallyl cyanamide is distilled under reduced pressure. It boils at 105–110°/18 mm.; at 128–133°/57 mm.; and at 140–145°/90° mm. There is a small residue of higher-boiling material. The yield of diallyl cyanamide, boiling over a five-degree range, is 90–97 g. (52–56 per cent of the theoretical amount based on the calcium cyanamide).

2. Notes

1. The lime nitrogen used in this preparation should be the crude, untreated, product sold as fertilizer under the name "Cyanamid." It contains approximately 55 per cent calcium cyanamide, 20 per cent calcium oxide, 12 per cent graphite, and small amounts of various impurities. Lime nitrogen should be protected from moisture when stored, in order to prevent slow polymerization to dicyanodiamide. It is advisable to use a fresh supply of lime nitrogen for this synthesis.

2. Stirring for one hour in the cold permits the relatively insoluble calcium cyanamide to react with sodium hydroxide and go into solution as sodium cyanamide. If the temperature is not kept below 25° during this time, there is some tendency for polymerization to dicyanodiamide.

3. A good grade of allyl bromide should be used.

4. No allyl bromide is recovered. When water is added to the alcohol distillate, which would undoubtedly contain any unused allyl bromide, none separates. The excess probably reacts to form allyl alcohol. However, no attempt has been made to isolate it.

5. This represents a general procedure for the preparation of dialkyl cyanamides; for example, di-*n*-butyl cyanamide has been prepared in a similar manner, in yields of about 50 per cent of the theoretical amount.

3. Other Methods of Preparation

The preparation of diallyl cyanamide by the above method has only recently been described in the literature.[1] However, other dialkyl cyanamides have been prepared by the following methods: the action of chlorocyanogen or bromocyanogen on dialkyl amines;[2] the reaction of dialkyl chloroamines with potassium cyanide;[3] the action of bromine on a mixture of dialkyl amines and potassium cyanide;[4] the action of alkyl halides on disilver cyanamide[5] and on disodium cyanamide.[6] Dimethyl cyanamide has also been prepared by the action of dimethyl sulfate on lime nitrogen[7] and on cyanamide.[8]

[1] J. Am. Chem. Soc. **46**, 1307 (1924); Swiss Pat. 104,101; Ger. Pat. 404,174; Chem. Zentr. **1925**, I, 1242; Versuche mit Diallylderivaten, Dissertation von Paul Graf, Eidgenossischen Technischen Hochschule, Zurich; page 27.

[2] Ann. **90**, 96 (1854); Ber. **32**, 1873 (1899).

[3] Compt. rend. **114**, 483, 1381 (1892); Bull. soc. chim. (3) **7**, 547 (1892); Ann. chim. phys. (7) **3**, 352 (1894).

[4] Compt. rend. **116**, 329 (1893); Bull. soc. chim. (3) **9**, 239 (1893); Am. Chem. J. **36**, 208 (1906).

[5] Ber. **10**, 427 (1877).

[6] Ber. **44**, 3149 (1911).

[7] Ber. **44**, 3150 (1911).

[8] Ber. **44**, 3165 (1911).

XVIII

2,3-DIBROMOPROPENE

$$CH_2BrCHBrCH_2Br + NaOH \rightarrow CH_2BrCBr{=}CH_2 + NaBr + H_2O$$

Submitted by R. LESPIEAU and M. BOURGUEL.
Checked by C. S. MARVEL, JOHN R. JOHNSON, and W. L. MCEWEN.

1. Procedure

A 500-cc. round-bottom flask is connected by a wide, bent glass tube to an efficient condenser, which is provided with an adapter leading into a 500-cc. receiving flask immersed in an ice bath. Two hundred grams (0.71 mole) of 1, 2, 3-tribromopropane (Note 1) and 10 cc. of water are placed in the reaction flask, and 50 g. (1.25 moles) of sodium hydroxide (Note 2) in small lumps (not pulverized) is added at once with shaking. The mixture warms up and the flask is immediately connected to the apparatus and heated directly by means of a Bunsen burner held in the hand. It is advisable to use a slightly luminous flame about 15 cm. high and to heat with a rotary motion, directing the flame against the sides of the flask.

The mixture is shaken occasionally, and the alkaline layer soon becomes partly emulsified. Heat is applied until vigorous ebullition occurs, whereupon a spontaneous distillation of the reaction product takes place (Note 3). When the reaction slackens, the flask is heated as before. The mass becomes solid as the volatile products are removed. This solid mass which is brownish in color, is heated until no more liquid distils (Note 4). The entire operation up to this point requires twenty to thirty minutes.

The distillate in the receiving flask separates into two layers: an upper layer of water; and a heavy layer of a colorless oil,

consisting of a mixture of 2,3-dibromopropene and unchanged tribromopropane. The distillate is transferred to a 500-cc. separatory funnel and thoroughly agitated with an additional 150 cc. of water (Note 5). The lower layer is decanted and found to weigh 140–145 g. It is subjected to a preliminary distillation under reduced pressure to separate most of the unchanged tribromopropane. All of the material that passes over below 95°/75 mm. consists of 2,3-dibromopropene containing a small amount of water and tribromopropane, and weighs 120–130 g. The residue in the distilling flask consists of unchanged tribromopropane (15–25 g.) (Note 6).

The crude product is dried over calcium chloride and fractionally distilled under reduced pressure (Note 7). The yield of pure, colorless 2,3-dibromopropene boiling at 73–76°/75 mm. is 105–120 g. (74–84 per cent of the theoretical amount). A small quantity of tribromopropane, usually about 5 per cent of the crude material, remains in the distilling flask (Note 6).

2. Notes

1. The crude tribromopropane, ootained as described on page 100, may be used without lowering the yield.

2. Potassium hydroxide may be used in place of sodium hydroxide, but it was found that the reaction is much more violent and irregular and the yields are somewhat lower. If potassium hydroxide is used, it is advisable to provide the receiving flask with a reflux condenser to avoid loss when the initial violent reaction occurs. Since the reaction is so rapid, it would be very dangerous to use more than 200 g. of tribromopropane in a single run with potassium hydroxide.

3. In the initial vigorous ebullition, about half of the material distils during a few minutes and it is necessary to wait for this reaction to slacken before continuing to heat the flask. If sodium hydroxide is used, the reaction is vigorous but not violent, and it is possible to use 600 g. of tribromopropane in a 1-l. flask in a single run without danger if the reaction flask is connected with the condenser by means of a wide tube. The yields in larger runs are as good as when smaller runs are made.

4. A small additional quantity of distillate may be obtained by partially evacuating the apparatus, after replacing the adapter and receiving flask by a 250-cc. distilling flask. The amount of material obtained in this way amounts to only 1–2 g. if the reaction flask has been properly heated. It is well to note that flasks which have been repeatedly heated with very strong alkalies become fragile, and care should be used not to reduce the pressure too greatly.

5. The dibromopropene and the wash water have a strong lachrymatory effect and should be manipulated carefully.

6. When a sufficient quantity of these crude residues of tribromopropane has been collected, it may be used for preparing 2,3-dibromopropene. If allowance is made for this recovered material, the yield of 2,3-dibromopropene is 82-87 per cent of the theoretical amount.

7. The separation of 2,3-dibromopropene from tribromopropane is effected easily since their boiling points are quite different.

Pressure	2,3-Dibromopropene	Tribromopropane
18 mm.	42– 43°	101–102°
75 mm.	75– 76°	140–142°
760 mm.	140–143°	219–221°

These substances may be distilled under atmospheric pressure with only slight decomposition, but the products become highly colored on standing.

3. Other Methods of Preparation

2,3-Dibromopropene has been prepared by the action of potassium [1] or sodium hydroxide [2] on tribromopropane, and by the action of metallic sodium on an ethereal solution of tribromopropane.[3]

[1] Ann. chim. phys. (3) **60**, 42 (1860); (7) **11**, 235 (1897); Ann. **154**, 371 (1870); Ber. **14**, 404 (1881); Bull. soc. chim. (4) **29**, 530 (1921).

[2] Ann. chim. phys. (7) **11**, 235 (1897); Bull. soc. chim. (4) **29**, 530 (1921).

[3] Ann. **156**, 168 (1870).

XIX

ETHYL ACETONE DICARBOXYLATE

$$CO_2HCH_2COCH_2CO_2H + 2C_2H_5OH + (HCl) \rightarrow CO_2C_2H_5CH_2COCH_2CO_2C_2H_5 + 2H_2O$$

Submitted by ROGER ADAMS and H. M. CHILES.
Checked by H. T. CLARKE and T. F. MURRAY.

1. Procedure

THE crude acetone dicarboxylic acid obtained from 700 g. of citric acid, as described on page 5, is treated with 700 g. of absolute ethyl alcohol (Note 1) to which has been added at least 130–150 g. of *dry* hydrogen chloride. The mixture is placed in a flask fitted with a stopper holding a calcium chloride tube and then is heated to 45°. It is kept in a water bath at 45° (bath temperature) with frequent shaking until all of the acid is dissolved (fifteen to twenty minutes). The solution is allowed to cool down to room temperature in the bath and finally to stand about twelve hours (Note 2).

The contents of the flask are then poured into 1300–1400 cc. of ice water, the ester layer separated, and the water-alcohol layer extracted twice with half its volume of benzene (700 cc.). The benzene extracts are added to the original ester, which has been separated. The total solution thus obtained is washed with about 400 cc. of 10 per cent sodium carbonate solution to remove the acid, then once with dilute sulfuric acid, and finally twice with 400 cc. portions of water (Note 3). The benzene is distilled on a water bath, and the ester is distilled under reduced pressure. A small low-boiling fraction comes over first and then the ester, which boils at 131–136°/9–10 mm. or 145–148°/17 mm.

(Note 4). The yield of product amounts to 284–315 g. (42–46 per cent of the theoretical amount based on the citric acid).

2. Notes

1. The directions given in the literature call for a smaller amount of alcohol than that given in the procedure but more consistent results were obtained with the method described.

2. The ester should be isolated from the reaction mixture after twelve hours. Longer standing causes a decreased yield.

3. One of the chief precautions which must be observed, if good yields are to be obtained, is thorough and careful washing of the benzene and ester mixture. If this is not done, decomposition occurs during distillation and the yields are lowered by about one-third.

4. The ester must be distilled under low pressure (under 20 mm.) or considerable decomposition occurs.

3. Other Methods of Preparation

This ester has been prepared by the esterification of acetone dicarboxylic acid [1] and of ethyl γ-cyanoacetoacetate.[2]

[1] Ann. **261,** 159 (1891); J. Chem. Soc. **75,** 809 Footnote (1899); **121,** 1642 (1922); Ann. **422,** 6 (1921).

[2] Compt. rend. **111,** 683 (1890).

XX

ETHYL ORTHOFORMATE

$$2CHCl_3 + 6C_2H_5OH + 6Na \rightarrow 2CH(OC_2H_5)_3 + 6NaCl + 3H_2$$

Submitted by W. E. Kaufmann and E. E. Dreger.
Checked by F. C. Whitmore and H. F. Herzog.

1. Procedure

In a 5-l. round-bottom flask fitted with an 80-cm. reflux condenser, are placed 3 l. of absolute alcohol (Note 1) and 490 g. (4.1 moles) of chloroform (Note 2). The flask is arranged for outside cooling by running water. To the solution, 207 g. (9 moles) of clean sodium cut into pieces which will conveniently drop through the condenser, is added during the course of about two hours. In order to add the sodium at this rate, the flask must be cooled during the addition. When the sodium has entirely reacted and the mixture has been cooled to room temperature, the sodium chloride which has separated is removed by suction filtration with the use of thoroughly dry apparatus (Note 3). The salt is washed on the filter with 200 cc. of absolute alcohol, and the washings are allowed to run into the main filtrate.

The solution is placed in a 3-l. flask fitted with an 80-cm. fractionating column (Note 4) and the excess chloroform and most of the alcohol are distilled off on a steam or water bath. The distillate is caught in a 2-l. suction flask protected from moisture by a drying tube. This distillation requires five or six hours. A mixture of chloroform and alcohol, weighing about 2000 g., is recovered and saved for the next run (Note 3). The liquid remaining in the flask is decanted from the small amount of salt which has separated, into a Claisen flask with a 30-cm. fractionating column (Note 5). The mixture is distilled at atmos-

pheric pressure. The fraction boiling below 85° is mainly alcohol and is discarded. An intermediate fraction of about 100 g., boiling at 85–140°, contains about one-fourth of the total yield. This may be fractionated but is best added to a subsequent run. The orthoformic ester is collected at 140–146° and weighs 120–140 g. (27–31 per cent of the theoretical amount). There is practically no higher-boiling material. Another distillation gives almost all the material boiling over a two-degree range.

After the first run, 400 g. of chloroform and enough absolute alcohol (800–1000 cc.) are added to the recovered chloroform-alcohol mixture to give a total volume of 3 l. The sodium is then added as before. After the excess of chloroform and alcohol has been distilled through the fractionating column, the intermediate fraction from the previous run is added before fractionating. The yield from such a run is about 200 g. (45 per cent of the theoretical amount).

2. Notes

1. Good absolute alcohol is essential. The use of alcohol of about 98 per cent gives only about two-thirds the yields obtained with absolute alcohol. Alcohol dried over lime usually runs about 98.5–99.5 per cent. A good method of obtaining a higher grade of absolute alcohol is to treat this alcohol with a little sodium. When the sodium has dissolved, the alcohol is distilled from a steam bath. Under these conditions, any trace of water that may be present on account of the equilibrum

$$C_2H_5OH + NaOH \rightleftarrows C_2H_5ONa + H_2O$$

remains in the concentrated solution of sodium ethylate and sodium hydroxide.

2. Enough chloroform must be used to keep the solution from being alkaline at the end of the reaction.

3. If care is taken to prevent moisture from getting into the recovered alcohol-chloroform mixture, this mixture may be used repeatedly. After it has been used four or five times, the yield begins to fall.

4. The long fractionating column used by Clarke and Rahrs

[Ind. Eng. Chem. 15, 349 (1923)] is a good one for use at this point. If such a column is not available, an 80-cm. reflux condenser without any water in it, may be used, connecting it at the top by means of a wide, bent glass tube to a condenser set downward for distillation.

5. A satisfactory type of flask for the distillation is that illustrated in Org. Syn. 1, 40.

6. The present method is better than that which uses dry ether as a solvent.

7. Yields equally as good as those mentioned in the above procedure are obtained by first preparing a sodium ethylate solution, using the quantities given above and adding this to an alcohol-chloroform solution. One decided disadvantage in this alternative procedure is that, unless a great deal more alcohol is used, the sodium ethylate solution tends to become semi-solid and cannot be introduced easily into the chloroform-alcohol solution. If one attempts to use recovered alcohol, containing chloroform, the sodium chloride which separates as soon as sodium is added, increases the tendency to become semi-solid.

8. The reaction is carried out best without stirring, thus allowing the sodium to float on top. In this way, the hydrogen escapes rapidly and little reduction of the chloroform takes place.

3. Other Methods of Preparation

Orthoformic ester has been prepared by the treatment of a mixture of chloroform and alcohol with sodium;[1] by the action of dry sodium ethylate on chloroform[2] or on an ether solution of chloroform;[3] by the action of alcoholic sodium hydroxide on chloroform;[4] and by the action of alcoholic hydrochloric acid on ethyl formimido ester[5] or its mercuric chloride double salt.[6]

[1] Jahresb. **1860**, 390; Ann. **152**, 164 (1869); Ber. **12**, 116 (1879); J. Soc. Chem. Ind. **42**, 430 T (1923).

[2] Ann. **92**, 346 (1854); Z. Chem. **1871**, 186.

[3] Ann. **240**, 193 (1887).

[4] J. prakt. Chem. (2) **48**, 231 (1893).

[5] Ber. **16**, 356 (1883); **31**, 1010 (1898).

[6] Am. Chem. J. **31**, 209 (1904).

Wood and Comley have recently published [7] a method for the preparation of orthoformic ester, in which sodium and chloroform are added alternately to the absolute alcohol. A few runs were made according to their directions but the results were not as satisfactory as those obtained by the procedure given above.

[7] J. Soc. Chem. Ind. **42**, 430 T (1923).

XXI

ETHYL OXALATE

$$\begin{array}{l} C(OH)_3 \\ | \\ C(OH)_3 \end{array} \rightarrow \begin{array}{l} CO_2H \\ | \\ CO_2H \end{array} + 2H_2O$$

$$\begin{array}{l} CO_2H \\ | \\ CO_2H \end{array} + 2C_2H_5OH \rightarrow \begin{array}{l} CO_2C_2H_5 \\ | \\ CO_2C_2H_5 \end{array} + 2H_2O$$

Submitted by JOSEPH KENYON.
Checked by C. S. MARVEL and A. B. ADAMS.

1. Procedure

IN a large evaporating dish is placed 252 g. (2 moles) of crystalline oxalic acid. The acid is heated on a steam bath for six to eight hours, with occasional stirring, until all the water of crystallization (72 g.) has been expelled. The oxalic acid which is almost anhydrous (weighing approximately 180 g.), is placed in a 1.5-l. round-bottom flask, *A*, containing 500 cc. of absolute alcohol and fitted up as shown in Fig. 1.

The flask *A* is heated by means of an oil bath maintained at 120–125° (Note 1); the mixed vapors of alcohol and water, passing through the fractionating column, are condensed in *D* and the moist alcohol is delivered under the surface of the alcohol contained in flask *B*. In flask *B* are placed 250 cc. of absolute alcohol and about 200 g. of freshly ignited potassium carbonate. Flask *B* is heated in an oil bath maintained at about 95–100°. The moist alcohol delivered to the flask *B* is dried by the potassium carbonate and subsequently returned as vapor under the surface of the liquid in flask *A*. The tube *C*, which is open to the air, acts as a safety valve to the otherwise closed system.

The reaction is run for about five hours. The excess alcohol is then distilled, the residue of ethyl oxalate is distilled under reduced pressure, and the fraction boiling at 98–101°/21 mm. is

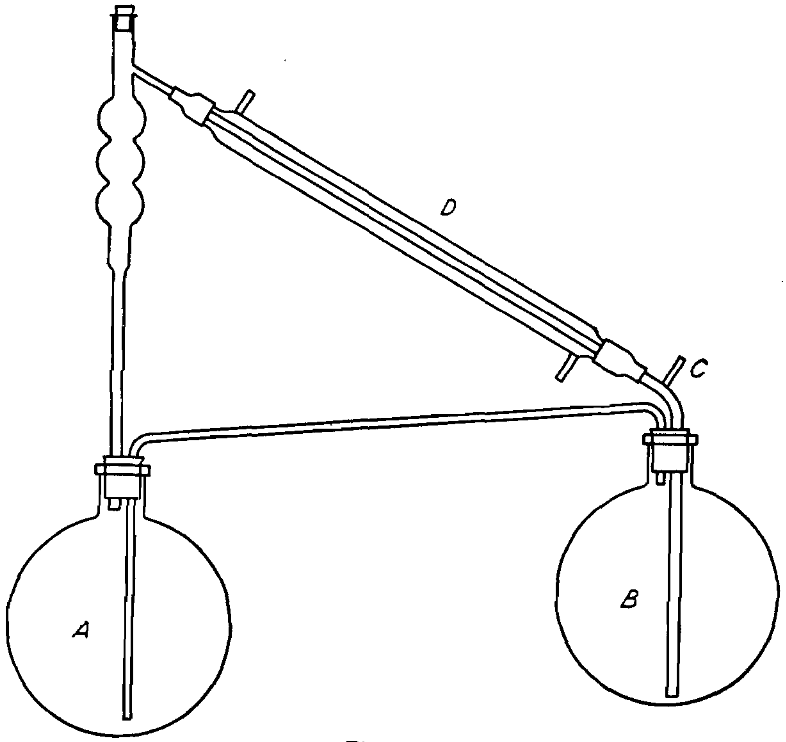


Fig. 1.

collected. The yield is 234–264 g. (80–90 per cent of the theoretical amount) (Note 2).

2. Notes

1. The temperature varies slightly with the length of the fractionating column. This temperature was noted when an ordinary two-bulb column (about 30 cm. long) was used.

2. A similar procedure may be used for the preparation of methyl oxalate. Instead of distilling this ester, it is better to cool the solution in an ice bath and separate the crystals of

methyl oxalate from the mother liquors in a basket centrifuge. The product thus obtained from 252 g. of crystallized oxalic acid weighs 120–125 g. Upon concentrating the mother liquors, cooling, and again centrifuging the mixture, a further crop of crystals weighing 30–35 g. may be obtained. Thus the total yield of methyl oxalate is 150–160 g. (63–67 per cent of the theoretical amount).

3. Other Methods of Preparation

The esterification of oxalic acid by the method of Clarke,[1] in which carbon tetrachloride is used to remove the water from the esterification mixture, is very satisfactory. However, the above procedure, which is based on the method of Frankland and Aston[2] for the preparation of ethyl tartrate, is very easily carried out and the yields are as good as those described by Clarke.

[1] Org. Syn. **2**, 22-26.
[2] J. Chem. Soc. **79**, 517 (1901).

XXII

d-GLUTAMIC ACID

Hydrolysis of Gluten from Wheat Flour $\longrightarrow CO_2HCH_2CH_2CH(NH_2)CO_2H$

Prepared by H. B. Lewis, H. M. Chiles, and G. J. Cox.
Checked by H. T. Clarke and C. J. Malm.

1. Procedure

Four kilos of wheat flour (Note 1) is placed in a large dish and worked with 3000 cc. of water to a stiff dough (twenty minutes). This is allowed to stand fifteen to twenty minutes and then the starch is washed out by gently kneading the dough in running water. The washing is continued until no more starch is carried off by the water and a rubbery mass of gluten, which is no longer sticky, remains. This washing requires twenty-five to thirty-five minutes (Note 2).

The wet gluten (about 1300 g.) is placed (Note 3) in a 5-l. round-bottom flask and covered with 1600 cc. of concentrated hydrochloric acid (sp. gr. 1.19). This reaction mixture is then warmed on the steam bath until the purple color disappears (about two hours). A reflux condenser is then attached and the solution is boiled gently over a flame for about eighteen hours. The hot solution is filtered with suction (Note 4) and the black residue of melanin is washed with about 200 cc. of water. The combined filtrate and washings are concentrated under reduced pressure until the volume is reduced to about 1500 cc. This solution is allowed to cool to room temperature and the crystals of glutamic acid hydrochloride filtered and washed with two 30-cc. portions of 95 per cent ethyl alcohol saturated with hydrogen chloride. The washings are discarded (Note 5) and the

mother liquor is concentrated to 500–600 cc. under reduced pressure; the second crop of crystals obtained on cooling is washed as before. The mother liquor is chilled in an ice-salt bath and saturated with hydrogen chloride; after standing over night in the ice-box, the crystals are filtered and washed as were the previous crops.

The combined crops of crystals are dissolved in the smallest possible amount of hot water (400–500 cc.). The solution is heated on a steam bath for about ten minutes, with 10 g. of decolorizing carbon (Norit) and filtered, whereupon a pale yellow solution is obtained (Note 6). The pure glutamic acid hydrochloride is again precipitated by saturating the ice-cold solution with hydrogen chloride and allowing it to stand over night in an ice-box. This crop of crystals is filtered and washed as before with alcoholic hydrogen chloride and finally with two 200-cc. portions of ether. On drying, 110–120 g. of glutamic acid hydrochloride is obtained. The mother liquor is concentrated to 250–300 cc. and saturated with hydrogen chloride, whereupon another crop of crystals weighing 25–50 g. is obtained (Note 7). The total yield is 140–145 g. The product melts at 202–204° on rapid heating (Note 8).

In order to obtain free glutamic acid, 183 g. (1 mole) of the above hydrochloride is dissolved in 750 cc. of distilled water and treated with 500 cc. of 2 N sodium carbonate solution. After standing over night, the free acid which has crystallized is filtered and washed with ice water until free of sodium chloride. The mother liquor and washings are united and concentrated to 300–350 cc. and again allowed to stand over night. The crystals so obtained are filtered and washed with ice-water. The total yield of colorless crystals which melt at 197–198° (corr.) is 109–120 g. (74–82 per cent of the theoretical amount).

2. Notes

1. The yield of glutamic acid hydrochloride varies somewhat with the brand of flour. The results described in this procedure were obtained with Gold Medal flour.

2. The water should have a temperatue of 20–25° in order to avoid unduly chilling the hands. Instead of washing the starch out of the gluten as described in the procedure, it is sometimes found convenient to place the flour in a muslin sack and wash the starch out through the meshes. This procedure usually requires a somewhat longer time.

3. The gluten is best introduced by first replacing all the air in the flask by steam, and then allowing the suction caused by the condensation of the steam to draw in the mass in one portion.

4. The filtrations are best made by using "filtros" plates. If ordinary filter paper is employed, at least three thicknesses must be used to prevent the acid solution from eating through the paper during the filtration.

5. The alcoholic washings contain much colored matter, and must not be added to the mother liquors.

6. The one treatment with decolorizing carbon should be sufficient if the operations have been carried out correctly. If not, several subsequent treatments may be necessary, in which case several short periods of treatment with small quantities give the best results. Continued heating with a large sample of bone-black is apt to deepen the color.

7. If the mother liquors are further concentrated, ammonium chloride separates; it is therefore advisable to discard them at this point.

8. If gluten flour (40 per cent gluten) is used instead of ordinary flour, the procedure is approximately the same. A 5-lb. sack* of gluten flour is washed to remove the starch. The wet gluten is placed in a 6-l. Pyrex flask with 3500 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and the hydrolysis is carried out as described above. After the hydrolysis and removal of the melanin by filtration, the solution is concentrated to about 1300 cc. The glutamic acid hydrochloride is then precipitated as already described. After two recrystallizations, the yield is 180–190 g. From the mother liquors a further yield of 45–50 g. is obtained, making a total of 225–230 g.

* This is the size of the sacks that are commonly obtained on the market.

"Glidine," a commercial diabetic food which is prepared from wheat flour and contains over 90 per cent of protein, may be used as a satisfactory source of glutamic acid. If this is used, it is not necessary to wash in order to remove the starch. From 1130 g. of this material, by hydrolyzing with 2500 cc. of concentrated hydrochloric acid and working up as before, 275–285 g. of glutamic acid hydrochloride may be obtained. Usually, the product from glidine is more difficult to decolorize. It has been found that an ether extraction of the hydrolysis mixture, after removal of the melanin, improves the color of the final product.

Glutamic acid may also be obtained from "Ajinomoto,"* a Japanese food product in powder form, consisting mainly of the monosodium salt of glutamic acid. The exact amount of this constituent may be determined by the Van Slyke amino nitrogen method or by igniting a sample of the material in a platinum crucible and titrating the residue of sodium carbonate. The calculated quantity of normal hydrochloric acid is added to a solution of the Ajinomoto in four times its weight of water, and then the solution is boiled with a little decolorizing carbon and filtered hot; the clear solution is allowed to stand over night in the ice-box and the crystallized glutamic acid is filtered and washed with ice-water. In this way, 72–73 per cent of the theoretical amount can be obtained; thus, 100 g. of Ajinomoto, found to contain 84 g. of monosodium glutamate, was dissolved in 400 cc. of water and treated with 500 cc. of normal hydrochloric acid and 54–55 g. of pure glutamic acid was obtained.

3. Other Methods of Preparation

d-Glutamic acid hydrochloride has been obtained by the hydrolysis of a large number of proteins. The common protein used in its preparation is gliadin from wheat.[1] Casein has also

* Ajinomoto may be obtained from S. Suzuki and Co., New York City.

[1] Abderhalden, Handbuch der Biochem. Arbeitsmethoden, **2**, 492 (1910); Ger. Pat. 301,499; Frdl. **13**, 202 (1917); Brit. Pat. 106,081; C. A. **11**, 3042 (1917); U. S. Pat. 1,255,390; C. A. **12**, 909 (1918); J. Am. Chem. Soc. **44**, 1801 (1922).

been recommended.[2] In general, the above procedure is like those already described in the literature but many details have been added.

d-Glutamic acid has been prepared from the hydrochloride by treating a water solution with strong alkalies,[2] alkali carbonates,[3] and ammonium hydroxide.[4] Hopkins [5] has shown that the addition of 6–8 volumes of alcohol to a concentrated water solution of glutamic acid hydrochloride will cause a slow precipitation of the free amino acid.

The preparation of *d*-glutamic acid from Ajinomoto was first described by Schmidt and Foster.[6] This is a very convenient method, but is more expensive than the preparation from flour.

[2] J. Am. Chem. Soc. **39**, 1429 (1917).

[3] Ger. Pat. 301,499; Frdl. **13**, 202 (1917); Brit. Pat. 106,081; C. A. **11**, 3042 (1917).

[4] Z. physiol. Chem. **77**, 76 (1912).

[5] Biochem. J. **15**, 293 (1921).

[6] Proc. Soc. Exptl. Biol. Med. **18**, 205 (1921).

XXIII

GLUTARIC ACID

$$CNCH_2CH_2CH_2CN + 2HCl + 4H_2O \rightarrow CO_2HCH_2CH_2CH_2CO_2H + 2NH_4C$$

Submitted by C. S. Marvel and W. F. Tuley.
Checked by H. T. Clarke and E. E. Dreger.

1. Procedure

In a 2-l. round-bottom flask are placed 100 g. (1.06 moles) of trimethylene cyanide (p. 103) and 500 g. (4.8 moles) of hydrochloric acid (sp. gr. 1.18). The mixture is refluxed for about four hours and then the solution is evaporated to dryness, preferably under reduced pressure. The dry residue, consisting of ammonium chloride and glutaric acid, is extracted with about 300 cc. of boiling ether. The ether solution is filtered and the residue is further extracted with two 100 cc. portions of boiling ether. The combined ether extracts containing the glutaric acid are evaporated (Note 1) to about 150–200 cc., whereupon the acid begins to crystallize. Then a liter of benzene (Note 2) is added and the mixture is heated until the glutaric acid dissolves. On cooling in an ice-salt bath, the acid crystallizes. The first crop weighs 103–105 g. (Note 3). The filtrate is concentrated to about one-third its original volume and cooled, whereupon a second crop of 13–14 g. of pure glutaric acid is obtained. The total yield is thus 116–119 g. (83–85 per cent of the theoretical amount) of a product melting at 97–98°.

2. Notes

1. Most of the ether can be recovered by concentrating the solution in a flask attached to a condenser set for distillation.

2. The glutaric acid may be directly extracted from the ammonium chloride with benzene, but this is less satisfactory on a small scale than is the procedure given.

3. When the benzene solution is chilled to 0° or lower, almost all of the glutaric acid separates in the first crop of crystals.

3. Other Methods of Preparation

Many methods have been mentioned in the literature for the preparation of glutaric acid. Of these, the only methods of preparative interest are: the hydrolysis of trimethylene cyanide with acids or alkalies,[1] the hydrolysis of methylene dimalonic ester [2] or methylene dicyanoacetic ester,[3] and the oxidation of cyclopentanone with nitric acid.[4] In this country the cheapness of trimethylene glycol makes it the best source for glutaric acid. The method described in the procedure is a modification of that originally described by Reboul.[5]

[1] Compt. rend. **82**, 1197 (1876); Ann. **182**, 341 (1876); Ann. chim. phys. (5), **14**, 501 (1878).

[2] Ber. **19**, 1055 (1886); **27**, 2346 (1894); Bull. soc. chim. (4) **11**, 382 (1912).

[3] J. Chem. Soc. **89**, 1460 (1906).

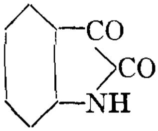
[4] Ann. **275**, 315 (1893).

[5] Compt. rend. **82**, 1197 (1876).

XXIV

ISATIN

$$C_6H_5NH_2 + NH_2OH + CCl_3CH(OH)_2 \rightarrow C_6H_5NHCOCH{=}NOH + 3HCl + H_2O$$

$$C_6H_5NHCOCH{=}NOH + H_2SO_4 \rightarrow$$  $+ NH_4HSO_4$

Submitted by C. S. MARVEL and G. S. HIERS.
Checked by J. B. CONANT.

1. Procedure

A. *Isonitrosoacetanilide.* In a 5-l. round-bottom flask are placed 90 g. (0.54 moles) of chloral hydrate and 1200 cc. of water. To this solution are then added, in order: 1300 g. of crystallized sodium sulfate (Note 1); a solution of 46.5 g. (0.5 moles) of aniline (Note 2) in 300 cc. of water to which 43 cc. (0.52 mole) of concentrated hydrochloric acid (sp. gr. 1.19) has been added to dissolve the amine (Note 3); and, finally, a solution of 110 g. (1.58 moles) of hydroxylamine hydrochloride (Note 4) in 500 cc. of water. The flask is heated over a wire gauze by a Meker burner so that vigorous boiling begins in about forty to forty-five minutes. After one to two minutes (Note 5) of vigorous boiling the reaction is complete. During the heating period, some crystals of isonitrosoacetanilide separate. On cooling the solution in running water the remainder crystallizes, is filtered with suction, and air-dried. The yield is 65–75 g. (80–91 per cent of the theoretical amount) of a product melting at 175°.

B. *Isatin.* Six hundred grams of concentrated sulfuric acid (sp. gr. 1.84) is warmed to 50° in a 1-l. round-bottom flask

fitted with an efficient mechanical stirrer and to this, 75 g. of dry (Note 6) isonitrosoacetanilide is added at such a rate as to keep the temperature between 60–70° but not higher (Note 7). External cooling should be applied at this stage so that the reaction can be carried out more rapidly. After the addition of the isonitroso compound is finished, the solution is heated to 80° and kept at this temperature for about ten minutes to complete the reaction. Then the reaction mixture is cooled to room temperature and poured upon ten to twelve times its volume of cracked ice. After standing for about one-half hour, the isatin is filtered with suction, washed several times with cold water to remove the sulfuric acid, and then dried in the air. The yield of crude isatin, which melts at 189–192°, is 47–52 g. (71–78 per cent of the theoretical amount). This product is pure enough for many purposes.

For purification, 200 g. of the crude product is suspended in 1 l. of hot water and treated with a solution of 88 g. of sodium hydroxide in 200 cc. of water. The solution is stirred mechanically and the isatin passes into solution. Dilute hydrochloric acid is then added, with stirring, until a slight precipitate appears. This requires about 290–300 cc. of an acid made by diluting one volume of concentrated hydrochloric acid (sp. gr. 1.19) with two volumes of water (Note 8). The mixture is then filtered at once, the precipitate is rejected, and the filtrate is made acid to Congo red paper with hydrochloric acid. The solution is then cooled rapidly and the isatin which separates is filtered with suction and dried in the air. The pure product thus obtained weighs 150–170 g. (Notes 9 and 10) and melts at 197–200° (corr.)

Isatin may also be crystallized from three times its weight of glacial acetic acid. In this case it is obtained in large brown-red crystals which melt at 196–197°.

2. Notes

1. Several runs were made in which the amounts of water and sodium sulfate were varied over a considerable range and this concentration was found to give the best yield of product of

good quality. The sodium sulfate seems to have more than a salting-out effect. If a saturated solution of sodium chloride is used no product is obtained.

2. Redistilled aniline boiling over a two-degree range was used in these experiments. The ordinary "pure" grade gives slightly lower yields.

3. If the aniline is not in solution, a considerable quantity of tarry material is formed during the heating period. No tar is formed when the method described is used.

4. The hydroxylamine hydrochloride used was the crude material prepared as described in Org. Syn. 3, 61. Preliminary experiments showed that this reagent must be present in considerable excess. Equally good results were obtained by using a solution of crude hydroxylamine sulfate which also contained sodium sulfate and ammonium sulfate with a little excess sulfuric acid. The hydroxylamine content was determined in this solution by titration with potassium permanganate solution. When this crude solution is used, the addition of sodium sulfate is not always necessary.

5. Longer heating of the reaction mixture gives a lower yield of dark-colored product.

6. If too much moisture is left in the isonitrosoacetanilide it is not easy to control the reaction with sulfuric acid.

7. The reaction does not start below 45–50° but becomes too violent above 75–80°. If the temperature becomes too high, the entire run is lost by charring. Stirring is needed to prevent local overheating.

8. The correct amount of acid that must be added to precipitate the impurities but not the isatin, will vary with different samples of crude isatin. If too much acid is added, some isatin comes down with the impurities. This may be saved and added to a subsequent run.

9. The yield of isatin is lower than for some of its derivatives. The explanation given in the literature is that some sulfonation occurs during the treatment with sulfuric acid, with corresponding loss of product.

10. This method can be applied successfully to other isatin

derivatives. Thus, under the same conditions, 54 g. of *p*-toluidine gives 75–77 g. (93–96 per cent of the theoretical amount) of isonitrosoaceto-*p*-toluidine melting at 162°. Eighty grams of this isonitroso compound treated as described under isonitrosoacetanilide, gives 65–68 g. (90–95 per cent of the theoretical amount) of crude 5-methyl isatin melting at 179–183°. This is purified as described under isatin by solution in sodium hydroxide and partial neutralization to throw out the impurities or by recrystallization from three parts of glacial acetic acid. The purified 5-methyl isatin melts at 187°.

3. Other Methods of Preparation

There are only two practical laboratory methods for the production of isatin, viz.: the oxidation of indigo,[1] and the condensation of aniline, chloral hydrate, and hydroxylamine salts, followed by the action of sulfuric acid.[2]

Of these methods, that of Sandmeyer[2] using aniline, chloral hydrate, and hydroxylamine salts, seemed most promising and has been studied in detail. The present method differs from that described by Sandmeyer in the use of hydroxylamine hydrochloride instead of a crude solution of hydroxylamine sulfate, and in the use of sodium sulfate to salt out the isonitroso compound.

[1] J. prakt. Chem. **24**, 11 (1841); **25**, 434 (1842); **95**, 177 (1865); **97**, 86 (1866); (2) **43**, 211 (1891); Ann. **53**, 10 (1845); **190**, 369 (1878); Jahresb. **1865**, 580; Ber. **17**, 976 (1884); Ger. Pat. 229,815; Frdl. **10**, 353 (1910).

[2] Helvetica Chim. Acta **2**, 237, 239 (1919); Brit. Pat. 128,122; C. A. **13**, 2375 (1919).

XXV

dl-METHYL ETHYL ACETIC ACID

$$C_2H_5CHBrCH_3 + Mg \rightarrow C_2H_5CH(MgBr)CH_3$$

$$C_2H_5CH(MgBr)CH_3 + CO_2 \rightarrow C_2H_5CH(CO_2MgBr)CH_3$$

$$C_2H_5CH(CO_2MgBr)CH_3 + H_2O \rightarrow C_2H_5CH(CO_2H)CH_3 + Mg(OH)Br$$

Submitted by Henry Gilman and H. H. Parker
Checked by H. T. Clarke and M. R. Brethen.

1. Procedure

In a 2-l. three-necked flask, fitted with a mechanical stirrer, condenser, thermometer well, and 500-cc. separatory funnel, is placed 48 g. (2 moles) of magnesium shavings. The shavings are then covered with 200 cc. of anhydrous ether. A solution of 274 g. (2 moles) of secondary butyl bromide (Note 1) in 300 cc. of anhydrous ether is dropped slowly on to the magnesium. Only a small amount should be added before the reaction starts. The well-stirred mixture is allowed to remain at room temperature during the addition which requires from two to three hours. When the secondary butyl bromide has all been added, the reaction is practically complete and further stirring or refluxing is unnecessary. An additional 500 cc. of anhydrous ether is added.

The reaction flask is then surrounded by an ice and salt mixture, and carbon dioxide is introduced above the surface with stirring. The rate of flow is regulated so that the temperature of the reaction mixture does not rise above $+2°$. The gas, obtained directly from a cylinder, is dried by passing through two wash bottles containing concentrated sulfuric acid and is admitted to the flask through an entry tube 10 mm. in diameter, at a height

of about 25 mm. above the surface of the ether solution (Note 2). The time required for the completion of the reaction varies from one to two hours. When the reaction is complete, the temperature falls below -5° and does not rise on increasing the rate of flow of carbon dioxide.

The reaction mixture is then hydrolyzed in the flask with 25 per cent sulfuric acid (Note 3). Cooling the solution with ice and water permits of rapid hydrolysis without danger of loss of the material through too vigorous refluxing. The mixture is transferred to a 2-l. separatory funnel and the ether layer separated. The water layer is extracted with three 100-cc. portions of ether. The combined ether extracts are washed with 25 per cent sodium hydroxide solution until all of the organic acid is converted to the salt and thus removed (Notes 4 and 5). About 300 cc. of the sodium hydroxide solution is required.

The alkaline extract is distilled to remove ether and other volatile impurities. It is then acidified with concentrated hydrochloric acid and the acid layer separated. The water layer is distilled from a 2-l. flask until no more oily acid comes over (Note 6). The distillate is saturated with salt and the acid layer separated. This water layer, together with the low-boiling fraction from the acid distillation, is distilled, and the distillate salted out as before.

The combined acid layers are placed in a 250-cc. distilling flask connected to an air condenser, which is in turn connected to a water condenser. This arrangement permits of very rapid distillation of the product which is collected at 173–175°. The yield of acid is 135–136 g. (66–67 per cent of the theoretical amount based on the quantity of secondary butyl bromide used) (Note 7).

2. Notes

1. The secondary butyl bromide must be of high purity. It may be prepared by the general method of preparing alkyl bromides, described in Org. Syn. 1, 1. Secondary butyl alcohol may be obtained from the Standard Oil Co. of New Jersey.

2. Troublesome clogging of the tube is avoided by having it above the solution instead of immersed in it.

3. The reaction product solidifies if it is allowed to stand too long in the reaction flask, thus causing difficulty with the hydrolysis. Time will be saved if the acid is added immediately after the addition of the carbon dioxide is completed. A rather concentrated acid solution is used in order to keep the volume of the water layer as small as possible.

4. The products of the reaction cannot be separated smoothly by fractional distillation prior to the extraction with alkali.

5. Considerable heat is evolved in the neutralization of the acid with the sodium hydroxide. The extraction can be carried on faster and without loss if the solution is cooled by the direct addition of ice. It is convenient to test the extracts with phenolphthalein to determine when all of the acid has been removed.

6. The methyl ethyl acetic acid may also be obtained by extraction of the acidified solution with ether. This method is not recommended, as small amounts of alcohol which are invariably present in this solvent, contaminate the product by the formation of the ethyl ester.

7. By the same general method, *n*-butyl bromide gives *n*-valeric acid in 64–65 per cent yield, bromobenzene gives benzoic acid in 70–71 per cent yield, and cyclohexyl bromide gives hexahydrobenzoic acid in 68 per cent yield.

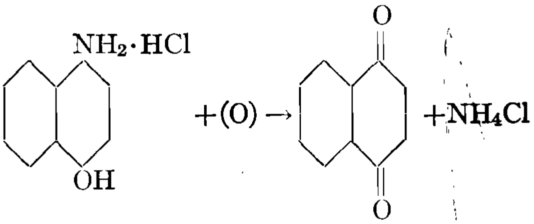
3. Other Methods of Preparation

dl-Methyl ethyl acetic acid may be prepared from methyl ethyl malonic ester by hydrolysis and subsequent heating of the methyl ethyl malonic acid.[1] The yield by this method, in the preparation of large quantities, is about 61 per cent of the theoretical amount based on the malonic ester used. The acid was first prepared by Saur [2] from methyl ethyl acetoacetic ester. It has also been made by oxidation of the corresponding aldehyde with chromic acid.[3]

[1] Ann. **298**, 167 (1897).
[2] Ann. **188**, 257 (1877).
[3] Monatsh. **7**, 56 (1886).

XXVI

1,4-NAPHTHOQUINONE



Submitted by J. B. CONANT and S. A. FREEMAN.
Checked by HENRY GILMAN and C. E. ADAMS.

1. Procedure

IN a 5-l. round-bottom flask are placed 180 g. (0.92 mole) of 1,4-aminonaphthol hydrochloride (Note 1), 20 g. of sodium bisulfite, and 2.5 l. of water. The mixture is heated over a ring burner until it just begins to boil and the resulting dark solution is filtered through a fluted filter paper in a 15-cm. glass funnel. When the filtrate has cooled to 55–65°, it is poured through a fluted filter into a solution of 135 g. (0.45 mole) of sodium dichromate, 140 cc. (2.5 moles) of concentrated sulfuric acid, and 300 cc. of water, in an 8-l. earthenware crock. The temperature of the acidified dichromate solution should be 40–50°; the addition of the sulfuric acid liberates enough heat to raise the temperature to this point. The solution is stirred by hand as the amine hydrochloride is added; a brown precipitate of the quinone forms immediately and the temperature rises somewhat (Note 2). The mixture is allowed to stand three hours and then is transferred to two 2-l. beakers, cooled in an ice bath to 10°, and filtered through a 15-cm. Büchner funnel. The precipitate

is washed with 1 l. of cold water in several small portions. The crude quinone thus obtained, when dried in the air, weighs 105–120 g. (71–82 per cent of the theoretical amount based on the aminonaphthol hydrochloride). It is crystalline and light brown in color (m.p. 120–123°) (Note 3).

The purification of the crude quinone is accomplished by sublimation in a current of steam under diminished pressure (Note 3). A 2-l. round-bottom short-neck flask is immersed as

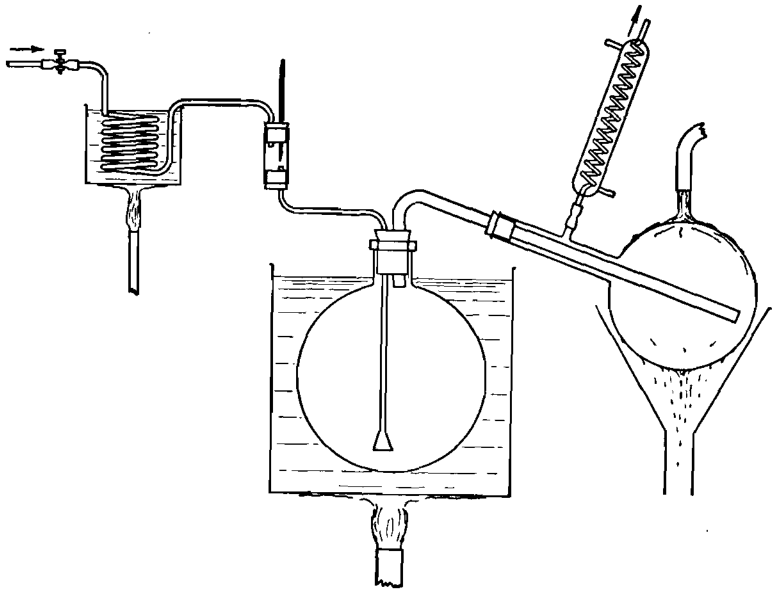


Fig. 2.

completely as possible in an oil bath (See Fig. 2). A rubber stopper carries a steam inlet of 5-mm. glass tubing, flared at the end and extending nearly to the bottom of the flask. A "goose-neck" of 20-mm. glass tubing is fitted into another opening in the stopper and extends well into the middle of the receiving flask, which is a 1-l. round-bottom distilling flask with the side tube pointing upwards and attached to a condenser. The flask is well cooled by running water. Dry steam is admitted into the apparatus through a piece of rubber suction tubing carrying a

screw pinchcock; the steam passes through two feet of lead tubing immersed in an oil bath, then through a tube carrying a thermometer (to record the temperature of the entering steam), and then directly into the flask (Note 4). The crude quinone from one run is made into a thin paste with a 10 per cent solution of calcium chloride, 15–20 cc. of solution being used for each 10 g. of quinone (Note 5). The paste is then introduced into the 2-l. flask which is rotated so that its entire inner surface is coated. The flask is placed in the oil bath which has been heated to 100°, the apparatus connected, and the temperature of the bath raised to 115–120°. The pressure is cautiously lowered by opening the connection to the suction. When all the water has evaporated from the flask, superheated steam at a temperature of 130° is admitted at such a rate that the distillate is adequately condensed. The pressure should be about 20 mm. The oil bath used for superheating the steam is kept at 200–220°, the temperature being controlled by the temperature of the thermometer in the steam. The quinone volatilizes rapidly and collects in the condenser. From time to time, the process is interrupted to empty the receiver; the distillation is continued until no more quinone distils. The distillate is filtered with suction and the quinone dried at room temperature in the air or under reduced pressure. The yield of pure quinone is 73–85 g. (50–58 per cent of the theoretical amount based on the amine hydrochloride). The pure quinone is lemon-yellow and melts at 123–124°.

2. Notes

1. The aminonaphthol hydrochloride (Org. Syn. 3, 7) need not be dried before using; the directions as here written correspond to the average yield from 200 g. of alpha-naphthol. The free base is unstable in solution, being easily oxidized by the air; the presence of bisulfite decreases this tendency.

2. The oxidation is carried out in warm solution to prevent the separation of the aminonaphthol hydrochloride on cooling. However, if the temperature is too high (above 85°) a black product is obtained.

3. The crude quinone thus obtained is light brown; the shade

varies somewhat with the experiment. It is about 80–90 per cent pure as determined by electrometric titration, and would be suitable for many purposes. It can be further purified by crystallization from benzene or ligroin. This is a difficult procedure, however, and always yields a light brown product and not the lemon-yellow material obtained by sublimation. Whether or not the difference in color is due to an impurity not removed by crystallization has not been determined.

4. If a considerable quantity of the quinone is to be purified, it is desirable to set up a superheating device made entirely of lead tubing and thus do away with the glass and rubber connections. The lead coil is made of 6-mm. lead tubing and is soldered by a T-joint on to a piece of 12-mm. lead tubing, which carries an opening for the thermometer at the top. The lower end of this tube is soldered to 10-mm. lead tubing which leads the steam into the flask arranged for the distillation.

5. The use of calcium chloride as a "binder" is necessary to prevent the crude quinone from being blown over with the steam. The temperature of the bath must not exceed 125°, as a very rapid decomposition occurs above this point. The speed of this rather troublesome purification process depends primarily on the surface exposed in the flask, provided this surface is in fairly good thermal equilibrium with the oil bath. Five to eight hours will usually be required for the sublimation of the amounts given in the directions.

3. Other Methods of Preparation

1,4-Naphthoquinone has been prepared by the oxidation of naphthalene,[1] 1,4-aminonaphthol,[2] 1,4-naphthylene diamine,[2] and 1,4-naphthylamine sulfonic acid.[3] Recent work[4] has shown that the oxidation of the 1,4-aminonaphthol is the most convenient method of preparation.

[1] Ann. **167**, 357 (1873); J. Chem. Soc. **37**, 634 (1880); **39**, 220 (1881). J. Russ. Phys. Chem. Soc. **16**, 417 (1884).

[2] Ann. **183**, 242 (1876); **286**, 70 (1895); Ber. **14**, 1796 (1881); J. prakt. Chem. (2) **62**, 31 (1900); J. Am. Chem. Soc. **46**, 1862 (1924).

[3] Ber. **12**, 2306 (1879).

[4] J. Am. Chem. Soc. **46**, 1862 (1924).

XXVII

m-NITROCINNAMIC ACID

$$(m)\ NO_2C_6H_5CHO + CH_3CO_2Na + (CH_3CO)_2O \rightarrow$$
$$(m)\ NO_2C_6H_4CH{=}CHCO_2H + CH_3CO_2H + CH_3CO_2Na$$

Submitted by F. K. THAYER.
Checked by ROGER ADAMS and A. B. ADAMS.

1. Procedure

IN a 200-cc. round-bottom flask, fitted with a reflux condenser, are placed 50 g. (0.33 mole) of *m*-nitrobenzaldehyde (Note 1), 40 g. (0.48 mole) of freshly fused sodium acetate, and 70 g. (0.68 mole) of acetic anhydride. The contents of the flask are well mixed and the mixture heated in an oil bath held at 180° for about thirteen hours. After the reaction product has been allowed to cool slightly, it is poured into 200–300 cc. of water and then filtered by suction (Note 2). After the solid has been washed several times with water, it is dissolved in a solution of 20 cc. of ammonium hydroxide (sp. gr. 0.9) in about 200 cc. of water. The solution of the ammonium salt, after filtering, is poured into a solution of 15 cc. of sulfuric acid (sp. gr. 1.84) in about 200 cc. of water (Note 3). The precipitated *m*-nitrocinnamic acid is filtered, redissolved in ammonium hydroxide, and again precipitated by pouring the solution into dilute sulfuric acid (Note 4).

After the last precipitation, the *m*-nitrocinnamic acid is washed with a little water and then sucked as dry as possible (Note 5). The product, which still contains considerable water, is dissolved in 250–300 cc. of boiling 95 per cent alcohol from which the nitrocinnamic acid crystallizes on cooling. The yield amounts to 47–49 g. (74–77 per cent of the theoretical amount).

The product is pale yellow and melts at 192–194°. If a purer product is desired, it may be recrystallized from benzene or alcohol (Note 6).

2. Notes

1. The *m*-nitrobenzaldehyde used was the technical grade and melted at 50–53°.

2. In one run, the product was extracted from the reaction mixture with benzene, removed from the benzene by a sodium carbonate solution, and this solution in turn acidified to obtain the *m*-nitrocinnamic acid. Neither the product nor the yield was as satisfactory by this method.

3. If acid is added to the solution of the ammonium salt, the precipitated *m*-nitrocinnamic acid carries down a considerable quantity of ammonium salts.

4. There is always a small amount of material that is insoluble in the ammonium hydroxide. This is removed by the second treatment.

5. The product is very difficult to dry. If it is removed from the filter after washing, several days are required for it to become dry. This dry product melts at about 190–193°.

6. The melting point of *m*-nitrocinnamic acid is given in the literature as 195° and 196–197°. Beilstein describes it as yellow needles. Alcohol is mentioned as a good solvent for recrystallization but experience in this work showed that benzene is also satisfactory, a white *m*-nitrocinnamic acid being obtained from this solvent.

3. Other Methods of Preparation

m-Nitrocinnamic acid has been prepared by the condensation of *m*-nitrobenzaldehyde with malonic acid in the presence of bases such as aniline and ammonia.[1] The best yield reported by this process is 72 per cent.

In the preparation from *m*-nitrobenzaldehyde, sodium acetate, and acetic anhydride,[2] no yield is mentioned in the literature.

[1] Ber. **31**, 2610 (1898).

[2] Ber. **11**, 1782 (1878); **13**, 2060 (1880); **46**, 3732 (1913); J. prakt. Chem. (2) **82**, 425 (1910).

XXVIII

NITROUREA

$$NH_2CONH_2 \cdot HNO_3 + (H_2SO_4) \rightarrow NH_2CONHNO_2 + H_2O$$

Submitted by A. W. INGERSOLL and B. F. ARMENDT.
Checked by HENRY GILMAN and C. C. VERNON.

1. Procedure

IN a 2-l. Erlenmeyer flask provided with a mechanical stirrer and thermometer, and surrounded by an ice-salt mixture, is placed 700 cc. of concentrated sulfuric acid. The stirrer is started, and when the acid is cooled to $-3°$ or below, 200 g. of dry, powdered urea nitrate is added in small portions at such a rate that the temperature does not rise above 0°. The addition will require about one-half hour. Stirring is continued for another half hour, the temperature being kept below $+3°$ (Note 1). Then the mixture is poured upon 1000 g. of ice.

The white, finely divided precipitate of nitrourea is filtered upon a 12-cm. Büchner funnel. A hardened filter paper (Note 2) is used in this operation and the nitrourea is pressed as dry as possible. The product is washed in the funnel with four portions of cold water just sufficient to cover it and pressed dry each time (Note 3). Then it is dried in the air (Note 4). By strongly cooling the filtrates, a further small amount of nitrourea may be obtained and added to the main portion. The yield of air-dried material is 120–150 g. (70–87 per cent of the theoretical amount). It melts with decomposition at 150–164° and is sufficiently pure for use in the preparation of semicarbazide (Note 5).

2. Notes

1. If bubbles of gas begin to be evolved while stirring, the mixture should be poured at once upon ice.

2. A hardened filter is necessary. Whatman's No. 50 is satisfactory.

3. Cracks appear when the nitrourea is filtered; hence, care must be taken that the water used for washing does not go through the cracks instead of through the material. If desired, the nitrourea may be removed from the funnel, made into a paste with about 800 cc. of cold water, and again filtered.

4. The product may be dried on a steam plate if the heating is not continued too long.

5. Various samples of nitrourea prepared in this way melt differently and therefore the melting point is not a suitable indication of purity. A uniform product can also be obtained by crystallizing half of the crude material obtained in one run from 1 l. of water at a temperature not over 55°, and using the filtrate to crystallize the second half. Even this recrystallized material does not have a definite melting point.

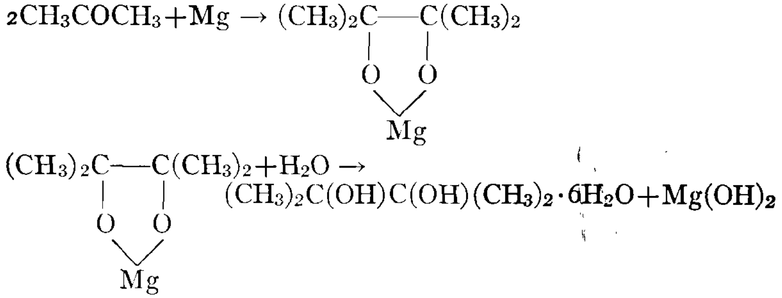
3. Other Methods of Preparation

Nitrourea has been made only by the action of concentrated sulfuric upon urea nitrate.[1] The procedure given above is essentially the same as that originally published by Thiele and Lachman.[2]

[1] Ann. **288**, 281 (1895); Rec. trav. chim. **31**, 21 (1912).
[2] Ann. **288**, 281 (1895).

XXIX

PINACOL HYDRATE



Submitted by ROGER ADAMS and E. W. ADAMS.
Checked by H. T. CLARKE and ROSS PHILLIPS.

1. Procedure

IN a 5-l. round-bottom flask, fitted with a stopper holding a separatory funnel and an efficient reflux condenser (Note 1) closed at the top with a calcium chloride tube (Note 2), are placed 80 g. (3.29 moles) of magnesium turnings and 800 cc. of dry benzene (Note 3). Through the dropping funnel is added gradually a solution of 90 g. of mercuric chloride in 400 g. (6.9 moles) of acetone (Note 4), carefully at first and then more rapidly after the reaction starts. The time of addition is about five to ten minutes (Note 5). Sometimes the reaction does not commence until a considerable proportion of the acetone solution of mercuric chloride has been added. In this case the reaction proceeds very vigorously when it does start and the flask must be cooled in running water to avoid loss through the condenser. As soon as the first vigorous reaction is over, a mixture of 200 g. (3.45 moles) of acetone and 200 cc. of benzene is added (Note 6). When the reaction slows down, the flask is heated on a water bath until no further reaction is evident (about two hours). During this time the magnesium pinacolate swells until it fills

the flask about three-quarters full. The flask is removed from the condenser and shaken until the reaction mass is well broken up (Note 7). The condenser is again attached and the heating continued for another hour.

Through the separatory funnel is then added 200 cc. of water and the reaction mixture is heated another hour. The flask should be shaken occasionally during this time. The reaction mixture is cooled to about 50° and filtered. The solid is returned to the flask and heated for ten minutes with a fresh 500-cc. portion of benzene to dissolve any remaining pinacol. The original filtrate and the second portion of benzene, after it is filtered from the magnesium hydroxide, are mixed and distilled to one-half the original volume in order to remove the acetone; the remaining benzene solution is treated with 300 cc. of water and cooled to 10–15°. The pinacol hydrate separates and after about thirty minutes it is collected on a suction filter and washed with benzene, or better, the mixture is centrifuged in a basket centrifuge. The pinacol hydrate air-dried at room temperature (Note 8), weighs 325–375 g. (43–50 per cent of the theoretical amount based on the magnesium used). The product melts at 46–47°. It is sufficiently pure for most purposes. Occasionally the product is slightly yellow. If such a product is dissolved in an equal weight of boiling water, treated with a little bone-black, filtered, and the filtrate cooled in ice, over 95 per cent of the material may be recovered in large white crystals.

2. Notes

1. The condenser should have an inner tube with a fairly large diameter (12–15 mm.) in order to take care of the acetone vapors during the vigorous reaction.

2. The reaction mixture must be guarded carefully from moisture throughout the reaction; if moisture is present the magnesium becomes coated with oxide or hydroxide and the reaction does not take place smoothly.

3. If a larger amount of benzene is used, the reaction is too slow in starting. Commercial benzene is satisfactory if it has been distilled and the first portion containing the water rejected.

4. The acetone used is the ordinary commercial grade dried over calcium chloride. The dryness of the acetone is important and determines the time required for the reaction to start; if perfectly dry (two to three days over calcium chloride with occasional agitation) the reaction starts at once.

5. The reaction should be allowed to proceed with the maximum speed without losing acetone through the condenser. If the reaction is made to run slowly, the yields are lower.

6. It is important that the second portion of acetone and benzene be added to the reaction mixture before the refluxing stops, as otherwise heat must be applied to start the reaction again.

7. Mechanical stirring is rendered somewhat difficult in the laboratory because the mass becomes almost solid at the end of the reaction. A centrifugal tube type stirrer (Org. Syn. **3**, 29) may be used and will give satisfactory results.

8. If dried at a temperature above that of the room, there is a tendency for the product to melt and for pinacol to be lost by volatilization.

3. Other Methods of Preparation

The only practical method for the preparation of pinacol hydrate is the reduction of acetone and the procedure described above is a modification of that of Holleman.[1] The more common reducing agents that have been used are magnesium amalgam,[2] aluminum amalgam,[3] sodium,[4] and sodium amalgam.[5] Electrolytic reduction has also been used.[6]

[1] Rec. trav. chim. **25**, 206 (1906).

[2] Compt. rend. **140**, 721 (1905); Bull. soc. chim. (3) **33**, 454 (1905); (4) **7**, 454 (1910); Rec. trav. chim. **25**, 206 (1906); Ger. Pat. 233,894; Frdl. **10**, 1000 (1911); Eng. Pat. 411; C. A. **5**, 3152 (1911); U. S. Pat. 1,039,739; 1,039,740; C. A. **6**, 3495 (1912); French Pat. 459,313; C. A. **8**, 2780 (1914).

[3] Ger. Pat. 241,896; Frdl. **10**, 1000 (1911); U. S. Pat. 1,068,777; C. A. **7**, 3195 (1913); French Pat. 459,313; C. A. **8**, 2780 (1914); Ital. Pat. 135,560; C. A. **9**, 2797 (1915).

[4] Ann. **110**, 27 (1859); **111**, 279 (1859); **114**, 54 (1860); Jahresb. **1873**, 340; Ber. **27**, 455 (1894); Ger. Pat. 248,252; Frdl. **10**, 999 (1912).

[5] Ann. **124**, 327 (1862); Ann. Suppl. **3**, 375, footnote (1865).

[6] Ger. Pat. 113,719; Frdl. **6**, 22 (1900); Ger. Pat. 252,759; Frdl. **11**, 539 (1912).

XXX

PINACOLONE

(Pinacoline)

$$(CH_3)_2C(OH)C(OH)(CH_3)_2 \rightarrow (CH_3)_3CCOCH_3 + H_2O$$

Submitted by G. A. Hill and E. W. Flosdorf.
Checked by C. S. Marvel and A. E. Gray.

1. Procedure

In a 2-l. round-bottom flask, fitted with a stopper carrying a dropping funnel and a connection to a condenser set for distillation, are placed 750 g. of 6 N sulfuric acid (Note 1) and 250 g. of pinacol hydrate (Note 2). The mixture is then distilled until the upper layer of distillate ceases to increase in volume (Note 3). This requires about fifteen to twenty minutes. The pinacolone layer in the distillate is separated from the water and the water is returned to the reaction flask. First, 60 cc. of concentrated sulfuric acid is added to the water, and then a second 250-g. portion of pinacol hydrate. The distillation is repeated. This process is repeated twice more until 1 kg. of pinacol hydrate has been used (Note 4).

The combined pinacolone fraction is dried over calcium chloride, filtered, and fractionally distilled. There is first a small low-boiling portion; then the pinacolone comes over at 103–107°; and finally there is a higher-boiling portion which yields more pinacolone on redistillation. The yield from a run, as described, is 287–318 g. (65–72 per cent of the theoretical amount). This product occasionally turns slightly yellow on standing, but redistillation removes the color with almost no loss of product.

2. Notes

1. Phosphoric acid (50 per cent) or hydrated oxalic acid may be used to bring about this rearrangement. When these reagents are used, the reaction mixture should be boiled for three to four hours. A yield of pinacolone corresponding to 60–65 per cent of the theoretical amount is thus obtained.

2. The pinacol hydrate is the unrecrystallized product obtained as described on page 87. The use of recrystallized pinacol hydrate increases the yield of pinacolone about 4 per cent.

3. An oily layer always remains behind in the distilling flask.

4. Larger or smaller runs of pinacolone may be made without materially affecting the yield.

3. Other Methods of Preparation

Pinacolone has been prepared by heating pinacol hydrate with dilute sulfuric acid or dilute hydrochloric acid;[1] by treating anhydrous pinacol[2] with concentrated sulfuric acid at 0°; by heating pinacol with 5 per cent oxalic acid[3] for twelve hours, or with 50 per cent tartaric, phosphoric, or oxalic acid[3] for three to four hours.

[1] Ann. **114**, 56 (1860); Bull. soc. chim. (4) **7**, 459 (1910); J. Am. Chem. Soc. **45**, 1559 (1923).

[2] Ber. **28**, 1364, footnote (1895); Chem. Zentr. **1906**, II, 496.

[3] Ber. **30**, 2266 (1897); Bull soc. chim. (4) **7**, 459 (1910).

XXXI

SEMICARBAZIDE SULFATE

$NH_2CONHNO_2 + H_2SO_4 + 6H$ (electrolytic) $\rightarrow$

$NH_2CONHNH_2 \cdot H_2SO_4 + 2H_2O$

Submitted by A. W. INGERSOLL, L. J. BIRCHER, and M. M. BRUBAKER.
Checked by HENRY GILMAN and L. C. HECKERT.

1. Procedure

A. *Apparatus:*

THE reduction is carried out in a 6×9 inch battery jar (Note 1), which is surrounded by a vessel suitable for a cooling bath. The bottom of the battery jar is covered with mercury, which serves as the cathode of the cell. The anode is a heavy lead coil separated from the catholyte by being suspended in a porous cup. This cup sets upon a support which holds it just above the cathode surface and does not appreciably diminish the latter (Note 2). The cathode is connected with the circuit by means of a glass tube partially filled with mercury and carrying a small piece of platinum wire sealed through the lower end. An efficient mechanical stirrer is provided in the catholyte. The current used in these experiments was 110 D.C., with a field rheostat, having a resistance of 8 ohms and a capacity of 20 amperes, for controlling the current. Any source of current supplying 30–110 volts and 15–20 amperes and any rheostat capable of carrying this current may be used. An ammeter reading to at least 15 amperes is connected in the circuit. Several reduction cells of the size described above may be run at one time, if they are connected in series. Fig. 3 shows the general set-up.

B. *Reduction of Nitrourea:*

After the apparatus is assembled, 600 cc. of 20 per cent sulfuric acid (Note 3) is placed in the battery jar, and the lead anode in the porous cup is also covered with acid of the same strength. The cell is surrounded by an ice-salt bath, the stirrer is started, and, while the solution is cooling, 50 g. of nitrourea (Note 4) is added to the catholyte. A thermometer is placed in the catholyte, and when the temperature drops to $+5^\circ$ the current is turned on as follows: with the rheostat set for maximum resistance, the current is switched on, then the rheostat is gradu-

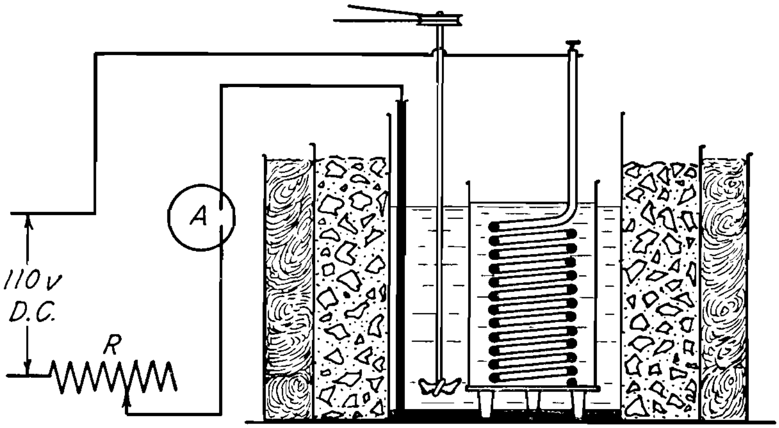


Fig. 3.

ally adjusted until the current flowing through the cell is about 0.06 amperes per square centimeter of cathode surface (Note 5). The cell must be efficiently cooled with ice and salt so as to keep the temperature at all times below 10° (Note 6). The reduction requires five to six hours. The nitrourea is quite insoluble, but gradually dissolves as it is reduced. The foam and clumps of solid are worked down into the liquid occasionally. When almost all the nitrourea is in solution, some of the catholyte should be drawn up with a pipette and used to wash down the nitrourea that adheres to the walls of the vessel. The reduction is continued for about ten to twenty minutes after the nitrourea has

dissolved. When the reduction is complete, as is indicated by a marked evolution of hydrogen, the current is shut off, and the porous cup is washed down with a little distilled water and removed. The solution of semicarbazide sulfate is removed from the cell and filtered (Note 7). The filtered solution is concentrated under reduced pressure on a water bath (Note 8) to a volume of 125–150 cc. Meanwhile, considerable semicarbazide sulfate will have crystallized. The mixture is cooled thoroughly in ice and the crystals are collected on a hardened filter paper, or better, on a filtros plate (see Note 5, p. 7), and washed several times with absolute alcohol to remove sulfuric acid. The crystals are dried on clay plate or paper. The yield is 50–57 g. (61–69 per cent of the theoretical amount) of a product melting at 144–145° with decomposition.

2. Notes

1. This is a commercial size. The internal diameter of these battery jars is 15–17 cm. Any sturdy glass vessel of the same dimensions may be used.

2. The lead anode should have about the same surface area as the cathode. In these experiments the porous cup used was 8 by 21 cm., but slightly larger sizes would do. A three-legged desiccator plate makes a convenient support for the cup. The latter should be immersed as deeply as possible in the catholyte, to decrease the resistance and consequent heating in the cell. It should not be more than 4–5 mm. thick, or the resistance will be too great and excessive heating will occur. Another convenient arrangement for the reduction cell is to divide the battery jar into two compartments by sealing in a diaphragm of thin cork-pine wood by means of paraffin. This offers very little resistance to the passage of the current and allows the reduction to be carried on very rapidly. A filtros plate may also be used as a diaphragm to separate the two solutions.

3. For runs of this size, sulfuric acid as dilute as 15 per cent may be used with good results. In larger runs or in runs using moist nitrourea, the 20 per cent acid is preferable.

4. Various grades of nitrourea (p. 85) may be used in the reduction without noticeably affecting the purity of the semicarbazide sulfate. In order to obtain the yields given in the procedure, the nitrourea was well washed, sucked dry on the filter, and air-dried. The moist material obtained after filtration is equally good (see Note 3). Runs in which 60–70 g. of nitrourea was used gave slightly lower yields than when 50 g. was used.

5. The current varies somewhat with changes in temperature and concentration and must be adjusted occasionally. If very efficient cooling can be had, currents as high as 0.07 ampere per square centimeter may be used. The current efficiency and speed of reduction are decreased with currents below 0.06 ampere per square centimeter. A current of 13.5 amperes was satisfactory for the cell described.

6. The yield falls off rapidly at temperatures above 10°. The control of temperature is much easier if the porous cup is immersed as deeply as possible in the catholyte (Note 2).

7. If another run is to be made immediately, the reduced liquor may be removed by means of a siphon or pipette. If it is decanted, a little vaseline rubbed on the edge of the vessel will *aid in pouring off the aqueous liquor from the mercury.*

8. The evaporation must be conducted on a water bath whose temperature does not exceed 50–55°, in order to avoid decomposition of the product. The evaporation may also be conveniently carried out by placing the solution in a beaker, warming to 50–55°, and blowing air over the surface of the solution. This takes a somewhat longer time but requires no watching.

3. Other Methods of Preparation

Salts of semicarbazide have been prepared by the action of potassium cyanate on hydrazine sulfate;[1] by the action of hydrazine hydrate on urea;[2] by heating hydrazine ammonium carbonate;[3] by the reduction of nitrourea with zinc dust and hydro-

[1] Ber. **27**, 31 (1894).
[2] Ber. **27**, 56 (1894).
[3] Ber. **44**, 3485 (1911).

chloric acid;[4] by electrolytic reduction with iron cathodes and ammonium chloride solution,[5] with tin cathodes and sulfuric acid solution,[6] with lead cathodes and hydrochloric acid solution,[7] with cathodes of copper, nickel, lead and mercury in hydrochloric or sulfuric acid solution.[8] The present procedure has been devised from the last-mentioned research.

[4] Ann. **288**, 312 (1895).
[5] J. Chem. Soc. **79**, 1326 (1901).
[6] Rec. trav. chim. **31**, 25 (1912).
[7] Jap. Pat. 39,219; J. Chem. Soc. **122**, (1) 723 (1922).
[8] J. Am. Chem. Soc. **47**, 393 (1925).

XXXII

1,2,3-TRIBROMOPROPANE

$$CH_2BrCH{=}CH_2 + Br_2 \rightarrow CH_2BrCHBrCH_2Br$$

Submitted by John R. Johnson and W. L. McEwen.
Checked by Roger Adams and L. T. Sandborn.

1. Procedure

A 1-l. round-bottom flask is provided with a mechanical stirrer, a dropping funnel, a calcium chloride exit tube, and a thermometer which reaches nearly to the bottom of the flask. In the flask are placed 181.5 g. (1.5 moles) of allyl bromide (Note 1) and 250 cc. of dry carbon tetrachloride (Note 2). In the dropping funnel is placed 80 cc. (1.56 moles) of bromine which has been washed once with an equal volume of concentrated sulfuric acid. The mechanical agitation is started and the flask is cooled in a mixture of ice and salt. When the temperature has fallen to $-5°$, the bromine is allowed to drop in slowly at such a rate that the temperature remains at about $-5°$ and never rises above $0°$ (Note 3). The addition of the bromine requires about one and one-half hours. The solution is usually orange-red in color at the end of the reaction, owing to the slight excess of bromine. It is allowed to warm up to room temperature with continuous stirring (about one-half hour) and is then transferred to a large separatory funnel. The flask is washed once with a 10–15 cc. portion of carbon tetrachloride.

A 500-cc. Claisen flask is arranged for distilling the solvent and the solution is dropped in from the funnel at such a rate that the flask is never more than two-thirds full. The Claisen flask is heated in an oil bath, and the carbon tetrachloride distils when the oil bath reaches about 120°. As much as possible of

the solvent is removed at atmospheric pressure by allowing the temperature of the oil bath to rise to 150°. The remainder of the carbon tetrachloride is removed under a pressure of about 20 mm. by collecting a fraction until the thermometer registers a sudden rise (temperature of the oil bath about 120°).

The residue in the distilling flask is practically pure 1,2,3-tribromopropane (Note 4) and boils at 100–103°/18 mm. On cooling in an ice-salt mixture and scratching vigorously, the tribromopropane solidifies to a mass of white needles, which melt below room temperature. The yield is 406–413 g. (96–98 per cent of the theoretical amount). If an absolutely colorless product is desired, it is advisable to collect the first few drops of distillate separately, since they may be slightly yellow. The product on long standing becomes yellow, but when the colored product is used in reactions it gives yields that indicate a high degree of purity.

2. Notes

1. Allyl bromide (Org. Syn. 1, 3) was dried with calcium chloride and distilled through a fractionating column. The portion boiling from 69.5–71.5° was collected.

2. Carbon tetrachloride was purified by distilling the commercial product and rejecting the first 10 per cent of the distillate, thus eliminating the water.

3. A yield of 93 per cent of the theoretical amount is obtained when the reaction is run at a temperature of 25–30°. At the higher temperature, there is a small amount of high-boiling product left in the flask after the final distillation.

4. The crude 1,2,3-tribromopropane which remains after complete removal of the carbon tetrachloride weighs 418–420 g. It is almost pure and can be used for a number of reactions without further purification.

3. Other Methods of Preparation

Symmetrical tribromopropane (glycerol tribromohydrin) has been prepared by the action of phosphorus pentabromide on

either epibromohydrin [1] or symmetrical dibromohydrin,[1,2] and by the addition of bromine to allyl bromide [3] or iodide.[4] It has also been obtained by heating glyceryl triacetate with hydrogen bromide dissolved in glacial acetic acid.[3a] 1,2,3-Tribromopropane is also formed by the action of bromine, usually in the presence of iron wire or aluminium bromide, upon *n*-propyl,[5] isopropyl,[6] trimethylene,[5] or propylene [5,7] bromides.

The method described in the procedure is essentially that of Perkin and Simonsen.[3a]

[1] Ann. **101**, 76 (1857).
[2] Ann. **154**, 369 (1870).
[3] Ann. **156**, 168 (1870); [(a)] J. Chem. Soc. **87**, 859 (1905).
[4] Ann. **104**, 247 (1857).
[5] Ber. **24**, 4245 (1891).
[6] Ann. **136**, 63 (1865).
[7] Compt. rend. **127**, 274 (1898).

XXXIII

TRIMETHYLENE CYANIDE

$$BrCH_2CH_2CH_2Br + 2NaCN \rightarrow CNCH_2CH_2CH_2CN + 2NaBr$$

Submitted by C. S. MARVEL and E. M. McCOLM.
Checked by H. T. CLARKE and E. E. DREGER.

1. Procedure

IN a 5-l. round-bottom flask fitted with a stopper holding a reflux condenser and a separatory funnel, are placed 294 g. (6 moles) of sodium cyanide and 300 cc. of water. The flask is heated on a steam bath until most of the sodium cyanide is in solution. This requires two to three hours. A solution of 500 g. (2.47 moles) of trimethylene bromide (Note 1) in 1 l. of 95 per cent alcohol is then added through the separatory funnel over a period of forty to sixty minutes. The mixture is refluxed for thirty to forty hours (Note 2) on a steam bath. Then the solvent is removed, preferably under reduced pressure. The residue, consisting of sodium bromide, sodium cyanide, and trimethylene cyanide, is extracted with 300–400 cc. of ethyl acetate, which dissolves the trimethylene cyanide and does not dissolve the inorganic salts. This solution is filtered and the salt washed once with about 100 cc. of ethyl acetate. The ethyl acetate is distilled at ordinary pressure (Note 3) and the residual liquid is distilled under reduced pressure. The yield of trimethylene cyanide boiling at 144–147°/13 mm. or 131–134°/10 mm. is 180–200 g. (77–86 per cent of the theoretical amount).

2. Notes

1. Larger runs seem to give slightly lower yields.
2. The yield is lower if the heating is continued too long, owing to partial hydrolysis of the cyanide.

3. Very little ethyl acetate is lost in this procedure if it is distilled at ordinary pressures. If it is not entirely removed before the pressure is reduced, considerable foaming occurs.

3. Other Methods of Preparation

The only practical method of preparation for trimethylene cyanide is the action of potassium cyanide on trimethylene bromide.[1]

[1] Compt. rend. **82**, 1197 (1876); **100**, 742 (1885); Bull. soc. chim. (2) **43**, 617 (1885); J. Chem. Soc. **55**, 702 (1889).

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